“A STUDY ON CLINICAL, BIOCHEMICAL, DRUG TROUGH LEVEL AND HISTOPATHOLOGICAL CORRELATION OF CALCINEURIN INHIBITOR (CNI) TOXICITY IN RENAL ALLOGRAFT RECIPIENT”

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DECLARATION

I, Dr.**Gandhimohan.R,** solemnly declare that the dissertation TITLED "**A STUDY ON CLINICAL, BIOCHEMICAL, DRUG TROUGH LEVEL AND HISTOPATHOLOGICAL CORRELATION OF CALCINEURIN INHIBITOR (CNI) TOXICITY IN RENAL ALLOGRAFT RECEPIENT"** is the bonafide work done by me at Department of Nephrology, Madras Medical College under the expert guidance and supervision of Dr. N.GOPALAKRISHNAN M.D., D.M., FRCP, Professor of Nephrology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of D.M. Degree (Branch III) in Nephrology.

Place: Chennai **Dr. Gandhimohan.R**

Date:

CERTIFICATE

This is to certify that the dissertation entitled "**A STUDY ON CLINICAL, BIOCHEMICAL, DRUG TROUGH LEVEL AND HISTOPATHOLOGICAL CORRELATION OF CALCINEURIN INHIBITOR (CNI) TOXICITY IN RENAL ALLOGRAFT RECIPIENT"**is a bonafide work done **Dr.Gandhimohan.R**, Department of Nephrology, Madras Medical College, in partial fulfillment of the University rules and regulations for award of D.M., Nephrology under my guidance and supervision during the academic year 2011 **–** 14**.**

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CONTENTS

Introduction

INTRODUCTION

The purpose of renal replacement therapy for End Stage Renal Disease patients was to prolong and maintain quality of life. Despite the many attempts to do renal replacement in early part of 20th century, the first successful renal transplant was done in 1954 by Murray among identical twins.

Introduction of calcineurin inhibitor in later part of twentieth century revolutionized the history of renal transplantation by reducing the short term morbidity and mortality. However the patients receiving calcineurin inhibitor were under the risk of calcineurin inhibitor nephrotoxicity in long run. The chronic nephrotoxic effects of calcineurin inhibitors associated with the renal parenchymal damage plays a major role in the pathogenesis of chronic renal dysfunction. Calcineurin inhibitor toxicity clinically characterized by tremor, hypertension, hypertrichosis and gum hypertrophy, biochemically by raising creatinine (graft dysfunction), hyperglycemia, hyperkalemia and hyperuricemia and histopathologicaly by isometric vacuolization, arterial nodular hyalinosis, striped fibrosis and interstitial atrophy.

The effect of toxicity was reversible in short term, became irreversible in long term. Lower dose results in graft dysfunction and rejection, higher dose results in toxicity because of its narrow therapeutic index (little difference between toxic and therapeutic doses). So it was mandatory to adjust its dosage according to measurements of the actual blood levels through therapeutic drug monitoring (TDM). The serum level of drug does not correlat with the degree of nephrotoxicity in most of the occasion because of its varied pharmacokinetics, narrow therapeutic index, individual sensitivity to toxic effects. .

Though there are few international studies on prevalence of calcineurin inhibitor toxicity and its clinico pathological correlation, a good study in this part of world is lacking . So, this study, attempt to find out the correlation among clinical, biochemical, drug trough level and histopathological features of calcineurin inhibitor toxicity.

Aim of the Study

AIM OF THE STUDY

To study the clinical, biochemical, whole blood trough level and histopathological correlation of calcineurin inhibitors (CNI) toxicity in renal allograft recipients

Review of Literature

CALCINEURIN INHIBITORS

Perhaps the most effective immunosuppressant drug, which served as the back bone of kidney transplant for past 2-3 decades. These comprise of Cyclosporine and Tacrolimus, although they are structurally distinct and combined with distinct immunophilin, cyclophilin and FK Binding Protein which act through common path way by inhibiting dephosphatase enzyme Calcineurin.

Calcineurin catalyzed dephosphorylation was required for entry of cytoplasmic component of nuclear factor of activated T cells into nucleus where it combined with its nuclear counter part and induces number of cytokine genes, especially interleukin–2, which play a major role in activation, differentiation and proliferation a T cells.

CALCINEURIN INHIBITORS-MECHANISM OF ACTION

In cytoplasm, cyclosporine binds to a cis-trans-peptidyl-prolyl-isomerase. Which was important in, folding proteins and peptides in to their native conformation (Immunophilin-protein that binds immunosuppressive agent: cyclophillin binds cyclosporine; FK-binding protein binds tacrolimus and rapamycin)[1]. Calcineurin-Immunophilin complex (i.e, cyclosporine- cyclophilin, tacrolimus – FK binding protein) binds to a calcium and calmodulin dependent phosphatase calcineurin. Which plays crucial role in transduction of calcium dependant signal.

Calcineurin, a phosphatase enzyme, which normally dephosphorylate the cytosolic part of nuclear factor of activated T cells in order to its entry into nucleus[2] and combined with nuclear part of activated T cells, which activates the promoter region of Interlukin L-2(IL-2) leading to its transcription[3], which results in reduction in its production, expression on cell surface and the resultant reduction in T cell activation and proliferation. Apart from its reduction in Interlukin-2 production, it also impairs the transcription of Interlukin-4(IL-4), Interferon(IFN)-gamma and tumour necrosis factor(TNF)-alpha.

The transcription of other genes, such as CD-40 ligand and the proto oncogenes H-ras and C-myc is also impaired. The stimulation of proto oncogene may be relevant to the cause of certain post transplant neoplasia.

Cyclosporine enhances the mRNA expression of Transforming Growth Factor (TGF)-beta in activated T cells[4] and constrain new DNA Synthesis. Patients on cyclosporine were found to have higher level of TGF-beta than patients on other immune suppressive drugs. TGf-beta inhibits IL-2 dependent, T Cell activation, and suppress the antigen specific T Cell proliferation. TGF-beta type 1 was a prosclerotic which play a major role in chronic cyclosporine nephrotoxicity. Cyclosporine apart from increasing TGF-beta, it increases the expression of its receptor in mesangial cells and activates the production of plasminogen activator inhibitor and fibronectin. Islem et al showed that anti TGF-beta antibodies prevents the certain changes of cyclosporine induce chronic nephrotoxicity. Thus the TGF-beta had the immunosuppressive role on its own and mediates immune suppressive effects of cyclosporine.

Thus the TGF-beta may play a central role in mediation of beneficial and detrimental effects of calcineurin inhibitor. Dentritic cell plays a major role in antigen presentation. Cyclosporine inhibits its migration, maturation, and impairs its antigen presenting capabilities[5].

CYCLOSPORINE

Cyclosporine is a small cyclic polypeptide of 11 amino acids in position 1, 2, 3, & 11 and molecular weight of 1200Kd. The cyclic polypeptide structure was necessary for its action. Cyclosporine is soluble only in lipids and organic solvents. First isolated by the department of microbiology at Sandoz (Switzerland) from two strains of imperfect fungai Cylindeocarpon lucidum booth and Trichoderma polysporum rifai as an antifungal agent[6].

Formulations

Cyclosporine available in oral and intravenous preparations. The original oil based sand-immune preparation had been replaced by microemulsion(Neo-oral). The oral preparation available in solution and soft gelatin capsules. Oral sand immune prepararion has variable time to peak(Cmax) concentration but averages 4 hours. Second peak appears in substantial portion of transplant patients. The oral bioavailability of cyclosporine was better. The peak cyclosporine level(Cmax) was higher and trough(Co) concentration correlates better with the systemic exposure as reflected by the area under the curve(AUC). Generic formulations of cyclosporine were available. FDA approved the generic formulations. But because of its varied absorption and narrow therapeutic index the bioequivalence stantardization of FDA for cyclosporine was more

rigorous. While changeover from branded to generic formulations, the drug level monitoring should be intensified. Since the pharmacokinetics and bioequivalence were different for sand immune and neo-oral its generic formulation should not be interchanged. Cyclosporine absorption was delayed and decreased by food. High and low fat meals decreases the area under the curve by 13% and maximum concentration by 33% when it consumed with in thirty minutes of drug intake. Cyclosporine distributed extensively in extra vascular compartment, at steady state the volume of distribution was 3-5L/Kg in kidney transplant recipients after Intra venous dosing.

Factors determining absorption

Individual patient

Type of transplant

Transplant age

Bile flow

Gastro Intestinal motility state

Type of formulations

Distribution

In blood, one third was bound to lipoproteins in plasma, remaining two third found in RBCs. So the whole blood levels were higher than plasma. Cyclosporine which bound with lipoproteins were easily enters

plasma membrane. Hence hypo cholesterelemia exaggerates toxicity and heper cholesterelemia reduces its toxicity. Hyperlipidemia was due to its affinity towards LDL receptor.

Metabolism

Cyclosporine was extensively metabolized by cytochrome P 450 3A in liver and gastrointestinal microsomal enzyme system[6]. It underwent first pass metabolism in liver and gastrointestinal tract by cytochrome P 450 3A and P-glycoprotein. The variability in its metabolism among individual was due to polymorphism[7] in cytochrome P 450 3A and P-glycoprotein. More than twenty metabolites of cyclosporine had been identified in bile, blood, feces and urine. Metabolites were inactive when compared to parent drug. Six percent of metabolites were excreted in urine. Only 0.1% of cyclosporine was excreted unchanged in urine. Since cyclosporine was neither excreted in urine nor removed by dialysis dose modification does not required in renal dysfunction. Cyclosporine was secreted in breast milk but in smaller quantity. Majority of its metabolites excreted through bile by liver, hence dose modification was imperative in liver disease. Half life was biphasic, averages 8.4-27 hours(range 4-50).

TACROLIMUS

Tacrolimus was a macrolide immuno suppressant isolated from fungus Streptomyces tsukubaensis in 1994 from Japan[8]. It was a 23 membered macrolide lactone. It was a neutral and hydrophilic compound. Initially it was used in liver transplant only. Approved by a FDA for kidney transplant in 1997, within a decade of approval its use had been raised to 67% in kidney transplant because of its potential immuno suppressive action.

Absorption

Tacrolimus absorption was variable. Bio availability varies from 5% to 95% (mean 25%). Reasons for reduced absorption were african/non-caucasians, diabetic patients and fatty food. Peak concentration attained after 0.5-1 hour. While took with food peak concentration delayed by 50-25% and the area under curve decreased by 25-40%. In intestine absorbed tacrolimus was metabolized by CYP P 450 3A, extruded into intestinal lumen by P-glycoprotein. Extruded drug again get reabsorbed[9]. Bile is not essential for tacrolimus absorption.

Distribution

In blood, tacrolimus was intensively bound to erythrocytes. Whole blood drug concentration significantly higher (4-14 time) than corresponding plasma level. In plasma most of the drug bound with alpha1 acid glycoprotein, globulin and albumin. In pediatric recipients a volume of distribution was higher than adult, because of increased permeability of membrane and reduced quality and affinity to plasma protein.

Metabolism

Tacrolimus was extensively metabolized by cytochrome P 450 3A4 in liver and intestinal epithelial cells by hydroxylation and demethylation. Metabolism of tacrolimus was highly variable because of cytochromeP 450 3A4 polymorphism. Expression of cytochrome P 450 3A4 varied from 10-100 fold in liver and 30-40 fold in intestine. The metabolites were one-tenth as active as tacrolimus. Its metabolites were seen in urine, feces and bile.

Elimination

More than 95% of tacrolimus was eliminated in bile[10]. Cholestasis increases the drug level. Urinary excretion accounts for 2.4%.

Factors affecting the pharmacokinetics of tacrolimus

Special patient population

In renal transplant, tacrolimus clearance was higher among live related kidney transplant recipient than cdaver transplant recipient because of low haematocrit and albumin. Diabetic patients shown 38% reduction in area under curve because of altered gut motility. Cystic fibrosis patients with pancreatic involvement in need of 40% higher dose because of decreased absorption due to pancreatic enzyme deficiency.

Hepatic dysfunction

Tacrolimus clearance was reduced up to 2-3 fold in patients with liver dysfunction. In hepatitis C virus infection drug level was higher because of alrtered cytochrome P system.

Renal function

Tacrolimus clearance was not altered by renal dysfunction and dialysis.

Age

Children required higher dosage because of differences in cytochrome P 450 3A, bowel length and P glycoprotein expression.

Sex

No difference between sex.

Race

African requires more dose than caucasians due to differences in expression of cytochrome P4503A and P glycoprotein expression in intestine and liver.

Haematocrit and albumin:

Reduction in haemotocrit and albumin results in lesser concentration of drug in whole blood.

Diurnal variation

Area under curve after morning dose was more than area under curve after night dose because of circadian effect on gastric emptying time and gastro intestinal perfusion.

Food

Effect of food depends on fat contents of food. Low fat content may delay the C-max.

Steroid

Steroid may induce cytochrome P 4503A and tacrolimus metabolism.

Diarrhea

Increased tacrolimus level because of loss of P glycoprotein which prevent extrusion of drug from gastro-intestinal epithelial cells.

PHARMACOGENETICS OF CALCINEURIN INHIBITORS(CNI)

Variability in cyclosporine Pharmacokinetics among individual was due to variability in exposure and function of cytochrome P 450 3A4 and P glycoprotein polymorphism[11]. P-glycoprotein polymorphism was due to ABCB1 gene Polymorphism. P-glycoprotein, a membrane protein found on membrane, act as exporter of intracellular xenobiotics, which is ATP dependent. In kidney P glycoprotein expressed on the luminal surface of proximal and distal tubular epithelial cells. Cyclosporine act as substrate for P glycoprotein, so if there is any defect in expression or function of P glycoprotein due to ABCB1 gene polymorphism cyclosporine accumulate inside the cell and lead on to nephrotoxicity[12]. According to Anglichem et al, sirolimus and cyclosporine competes for P glycoprotein. So if used in combination sirolimus cause cyclosporin accumulation and nephrotoxicity.

Transcriptional analysis revealed that epithelial mesenchymal trans formation(EMT) and endoplasmic reticulum stress are the two main mechanism which cause CNI nephrotoxicity. In vitro studies revealed that cyclosporine induced EMT changes in proximal tubular epithelial cells through TGF-beta up regulation. Vimentin expression had been increased in rats treated with cyclosporine.

Endoplasmic reticulum stress is due to accumulation of mis-folded proteins within endoplasmic reticulum. It has been proved by in vitro studies. Progress in whole genome studies, molecular biology and functional genetics will throw further light on this area in future.

CALCINEURIN INHIBITORS-DRUG INTERACTION

Cyclosporine was degraded by hepatic cytochrome P450. Durgs which enchances the ability of cytochrome P450 reduces the concentration of cyclosporine and drugs that inhibit the cytochrome P450 increases the concentration of cyclosporine level[13] in blood.

Durgs that decreases the calcineurine level (cytochrome P450 inducer):

Anti tuberculous drugs

Rifampicin (marked reduction)

Pyrizinamide

Ethambutol

Anticonvulsants

Barbiturates (marked reduction)

Phenytoin

Primidone

Carbamazepine (mild reduction)

Modafinil (mild reduction)

Oxcarbazepine (second generation – mild reduction)

Antibiotics:

Nafcillin

Intravenos trimethoprim

Intravenos sulphadimidine.

Imipenem

Cephalosporin

Terbinafine

Others:

St.John’s wort (Hypericum perforatum) – Herbal anti depressant

Ticlodipine.

Corticosterods

Drugs that increases calcineurin level(cytochrome P450 inhibitor):

Calcium channel blocker:

Verapamil (40% reduction in CNI dose)

Diltiazem (40% reduction in CNI dose)

Amlodipine

Nicardipine

Nifedepine (minimal effect)

Felodipine (minimal effect)

Anti fungal

Ketoconazole (80% reduction of CNI dose)

Fluconazone

Itraconazole

Voricanozole

Antibiotics:

Erythromycin

Clarithromycin

Azithromycin (conflicting reports)

Anti retroviral drugs:

Protease inhibitor (Ritonavir)

Hormones:

Oral contraceptive

Anabolic steroids

Testosterone

Nor ethisterone

Danazol

Somatostatin

Other drugs:

Amiodarone

Carvedilol

Allopurinol

Bromocriptine

Chloroquine

Grape fruit juice (cytochrome P450 inhibitor)

Drugs that increases absorption:

Metoclopromide

Grape fruit juice

Drugs that exaggerates CNI nephrotoxicity.

Potentially nephrotoxic drugs should be avoided while patient on calcineurine inhibitor. Can be used with appropriate monitoring

Amphotericin

Aminoglycoside

NSAID

ACEI / ARB

CALCINEURIN INHIBITORS TOXICITY

Despite the advantages of calcineurin inhibitors in solid organ transplantation and other diseases, its side effects hampers the long term graft and recipient morbidity and mortality[14].

Renal

Acute calcinurin inhibitor nephrotoxicity

Chronic calcinurin inhibitor nephrotoxicity

Hepatic

Neurologic

Cardiovascular

Dermatologic

Dental

Metabolic

Lipid abnormality

New Onset Diabetes Mellitus

Hyperuricemia and Gout

Infection and malignancy

Thromboembolism

Renal toxicity

Acute calcineurin inhibitor nephrotoxicity

Acute arteriolopathy

Tubular isometric vacuolization

Thrombotic microangiopathy

Chronic calcineurin inhibitor nephrotoxicity

Interstial fibrosis and tubular atrophy (typically stripped)

Medial arteriolar hyalinosis

Glomerular capsular fibrosis

Global glomeruloselerosis

Focal segmental glomerulo sclerosis

Juxta glomerular apparatus hyperplasia

Tubular micro calcification

Nephrotoxicity was the major side effect of these drugs. Initial experiences revealed that it was reversible hemodynamic changes. In 1984 Meyers et al demonstrated that progressive and irreversible changes also occurs in kidney resulting in tubular and interstial injury and glomerulosclerosis. The reversible changes were known as acute calcineurin inhibitor nephrotoxicity. Irreversible changes were known as chronic calcineurin inhibitor nephrotoxicity

Acute arteriolopathy (vascular effect)

In 1985, Murray et al shown that afferent arteriolar constriction[15] was caused by cyclosporine, which result in acute reversible functional impairment of glomerular filtration. This is due to imbalance between vasoconstrictor and vaso dilator substances produced by cyclosporine (vasoconstrictor : endothelin, rennin angiotensin ; vasodilator : prostacyclin, prostaglandin $E_{2,}$ nitrous oxide) and free radical formation. Endothelin was a potent vaseconstrictor widely released in the kidney and vascular bed. The role endothelin in acute reversible vasoconstriction was established by the obliteration of these vasoconstrictive effect by anti endothelin antibodies[16]. Apart from direct afferent arteriolar vasoconstriction it also stimulates the rennin angiotensin system by recruiting rennin secreting cells in juxta glomerular apparutus and results in increased rennin production. Rennin enhances angiotensin II and

reduces blood flow. Thus it becomes vicious cycle. On chronic use of cyclosporine it results in juxta glomerular cells hyperplasia. The molecular mechanism by which cyclosporine recruits the renin secreting cells in afferent arterioles and increases renin secretion was currently not known. Cyclosporine and tacrolimus inhibits endothelium mediated nitrous oxide synthesis thus by inhibits vasodilation. Cyclosporine induced vasooclusion results in hypoxia, free radical formation and super oxide production. By farming peroxynitrite, super oxide decreases nitrous oxide bio availability.

Tubular effects (toxic tubulopathy)

Histologically isometric vacuolization[17] in tubular epithelial cells by cyclosporine was due to enlargement of endoplasmic reticulum and increased lyzosomes. These vacuolization was found with cyclosporine and tacrolimus in the absence of renal dysfunction. Renal dysfunction may found in the absence of morphological feature. Recent studies revealed that these vacuolization also occurs in renal ischemia (on tubular epithelial injury due to intra venus administration of hyper osmotic fluid (manitol, inulin, glucose). These vacuoles were varying in size (in contrast to calcineurin induced) and called as osmotic nephrosis. Apart from ischaemic insult direct role of calcineurin inhibitors also postulated, inclusion bodies were also expressed as on tubular epithelial cells, which

are nothing but giant mitochondria and auto lysozomes. Even though mechanism of inclusion body formation was not known the important effect of cyclosporine on mitochondrial function was proved. How ever inclusion bodies also found in ischemic injury and preimplantation donor biobsies.

Thrombotic microangiopathy

It was a distinct form of calcineurin inhibitor nephrotoxicity, uncommon but serious histopathologically characterized by intra capillary platelet thrombi, intimal wall thickening, necrosis and luminal occulusion. This lesions may in patchy distribution and variable severity. Mechanism postulated was endothelial damage caused by ischemia due to direct calcineurin inhibitor effect on endothelium. The concomitant increased platelet aggregation, plasminogen activator inhibitor activity and pronecrotic activity of calcineurine inhibitor on endothelium eventually lead to development of thrombotic micro angiopathy.

Chronic CNI nephrotoxicity

Calcineurin inhibitors not only induces acute reversible nephrotoxicity but associated with chronic reversible nephrotoxicity, which involves vessels (arterial hyalinosis), interstitium (interstitial fibrosis & tubular atrophy) and glomeruli (focal segmental glomerulo

selerosis, thickening & fibrosis of bowman's capsule). Nankivell et al shown that 15 years after transplantation lesions suggestive of irreversible damage were seen in all recipient. However these features were may be due to rejection, infection, hypertension, diabetes mellitus, drugs and aging. Since this study did not have control arm. Cycloscorin related haemodynamic changes and direct toxicity was thought to play a role.

Vascular effect

Afferent arterioles nodular hyalinosis was regarded as a hall-mark of CNI nephrotoxicity. Which was due to replacement of reactive smooth muscle cells by focal or circular protein (hyaline) deposits at the peripheral part of afferent arteriole wall, eventually results in narrowing of afferent arteriolar lumen. The molecular mechanism behind this was not well elucidated.

Tubulo-interstitial effect

Cyclosporine induced luminal narrowing, hypoperfusion, hypoxia and formation of reactive oxygen species results in cell death by apoptosis. Catalase, a enzyme which catalyse reactive oxygen species, antagonize the effects of cycloscorine induced apoptosis in vitro. Second hypothesis was the direct injury to the epithelial cell by cycloscorine

which results in accumulation of intra-cellular reactive oxygen species, lipid peroxidation products along with an altered glutathione redox state.

Cyclosporine induced upregulation of TGF – beta play a major role in the formation of chronic interstitial fibrosis and tubular atrophy. TGF – beta promotes interstitial fibrosis by increasing the production of extra cellular matrix protein and decreasing the degradation. In addition TGF - beta promotes epithelial mesenchymal transition, which results in loss of epithelial phenotype. Which results in loss of epithelial polarization, denovo expression of dysregulated acting over smooth muscle, loss of intercellular adhesion through down regulation of E-cathedrin, destruction of basement membrane and increased cell invasiveness. Remuzzi et al shown that hyper aldosteronism secondary to salt depletion and RAS activation increases the production of TGF – beta and reactive oxygen species, which cause interstitial fibrosis. Apoptosis of tubular and interstitial cells aggravated by direct toxic effect of CNI on apoptosis gene. In addition cyclosporine competitively inhibit the P-glycoprotein on luminal side of tubular epithelial cells and cause accumulation of toxic substances inside the cell.

Glomerular effects

Chronic CNI intake results in glomerulosclerosis secondary to ischaemia induced by arterial hypertension. Tubular damage results in atubular glomeruli which was shrunken in size and shows periglomerular fibrosis. In addition CNI can cause secondary focal segmental glomerulosclerosis due to either arteriolar hyalinosis or global glomerulosclerosis.

Non specificity of histlogic findings

Morphological findings in CNI toxicity were not specific to CNI. It also found in other diseases. So called specific lesions such as tubular vacuolization and arterial hyalinosis also seen in other diseases.

Hypertension

Impaired renal haemodynamics due to afferent arteriolar vasoconstriction by CNI results in sodium, water retention and hypertension. In addition stimulation of sympathetic system, activation of RAS and suppression of atrial natriuritic peptide impairs the diuretic and natriuretic response to volume overload. Hypertension was tend to be less marked in tacrolimus on comparison with cyclosporine primarily due to less peripheral vasoconstriction.

Hyperkalemia

Hyper/normokalemia, mild hyperchloremic acidosis and patients intact ability to secrete acid urine was usual features of CNI toxicity. It was due to inability to excrete acute potassium load due to defect in production of aldosterone or to its post receptor response. Exaggerated by concomitant acetyl choline esterase inhibitors, angiotension receptor blocker.

Hypomagnesemia & hypocalcemia

It was due to increased urinary loss in patients on CNI due to down regulation of specific transport proteins.

Hyperuricemia

Impaired uric acid secretion due to cyclosporine induced direct tubular defect which may lead on to gout.

Hepatic

Mild transaminites and mild hyper bilirubenemia may occur in 50% of patients on cyclosporine, due to defect in bile secretion, there may be any morphological changes. Cyclosporine use was associated with cholelithiasis due to increased lithogenecity. Gastro intestinal side effects such as anorexia, nausea, vomiting, diarrhea and abdominal discomfort occurs more with tacrolimus than cyclosporine.

Neurologic

- Coarse tremor, dysesthesia, headache, insomnia (dose and blood level related)
- Cognitive impairment coinciding with peak drug level.
- Occasional seizure, full blown leukoencephalopathy and bone pain.
- Disabling pain, hallucination, seizure, cerebellar ataxia and motor weakness.

Dermatological

- Hypertrichosis – obvious in dark haired girls.
- Eye brow prominence

Dental

Gingival hyperplasia due to fibroblast proliferation and collagen deposition was common in cyclosporine and exaggerated by poor oral hygiene and concomitant calcium channel blocker. Severe gingival hypertrophy may require gingivectomy and switch to tacrolimus

Metabolic

Glucose intolerance

Impaired glucose tolerance and new onset diabetes mellitus was more common with tacrolimus than cyclosporine, reason being the more concentration of FK binding protein than cyclophilin in islets,. Steroid

may exaggerate the cyclosporine induced glucose intolerance. Glycosuria may be result in direct cytoplasmic injury to tubules. Risk factors were obesity, family history of diabetes and hepatitis C virus.

Hyperlipedemia

Cyclosporine was implicated in post transplant hypercholesterolemia. The mechanisms were LDL receptor binding by cyclosporine, defective LDL feed back control by liver and altered bile acid synthesis.

Hyperuricemia

Cyclosporine induced tubular injury results in impaired uric acid secretion which results in accumulation of uric acid in blood and gout. It was aggravated by concomitant diuretic use. This was more with cyclosporine than tacrolimus.

Infection and malignancy

Infections and malignancies were inevitable following immunosuppressant use in organ transplantation. Infection more coincides with level of drugs in blood. More incidence of skin cancer had been reported with cyclosporine use. Cyclosporine can promote tumor progression, which was independent of its effects on the immune response.

MONITORING OF CALCINEURIN INHIBITORS

Monitoring of cyclosporine level was essential, due to inter and intra patient variability, lower level results in rejection, higher lever results in toxicity, co prescribed drugs may result in alteration of cyclosporine level. Recovery from uraemia in early post transplant period results in increasing absorption so it needs close monitoring. Because of availability of various assay methods, option of multiple matrices (plasma, whole blood) and variable correlation with time of drugs intake results in much confusion.

Trough monitoring

Even though monitoring at the trough, before administering next dose (Co level) was traditional and convenient, the efficacy was questionable. Area under curve calculation using multiple blood sample assessment will be more effectively reflect the exposure of patient to drugs. Correlation with nephrotoxicity was not linear. Correlation with episode of acute rejection was also poor[18].

Area under curve(AUC)

Even though calculation of AUC by assessing multiple blood samples in 0-12 hrs was more accurate, the process was largely impractical. Gaspais et al shown that AUC by 1, 5, 8 & 11hrs sample allowed accurate monitoring. Malhati et al shown that since microemulsion form of cyclosporine absorption variability limited to first

four, the AUC 0-4 hrs, will correlate with clinical outcomes. But, it also requires multiple sampling. So the ideal strategy should be single point measurement. Monitoring two hours level (C_2) was considered an ideal surrogate marker[20].

Two hours monitoring

Most accurate one point prediction of AUC 0-4 hrs, was the C_2 level (sample taken two hours after last dose) and it showed less variability than either Co or C_1 according to international renal transplantation study group. Canadian neoral renal transplantation study group's result shown that C_2 level of more than 1500 micro gram per liter at 2 weeks of post transplant period correlate significantly with lower rejection rates. According to Helsinki groups the rate of acute rejection was not significantly influenced by either C_0 or C_2. C_2 Monitoring allowed a dose reduction in 34% of patients compared to 14.3% of patients in Co monitoring. In spite of dose reduction there was no improvement in renal function during 40 months follow up. Despite those controversial issues at the moment, trough (C_0) remain the standard method of monitoring.

Cyclosporine assays:

High perfusion liquid chromatography(HPLC) method:

Despite the availability of several methods to measure the Cyclosporine level HPLC was the gold standard, because of its ability to

measure parent compound only. However it was expensive, labour intensive and not available in all centers. Its accuracy in lower plasma level was less précised.

Immunoassay:

1. Non specific polyclonal immunoassay.
2. Non specific monoclonal immunoassay.

Immuno assay are based on monoclonal / polyclonal anti bodies against cyclosporine. Monoclonal immune assay were largely replaced HPLC because it can be done on automated chemistry analyzers.

Fluorescence Polarization Immune Assay was the most common immune assay used now a days. But it overestimate by 45% because significantly cross reacts with cyclosporine metabolites.

Rapid Liquid Chromotography – mass spectrometry method was a newer method, which had been used in oxford laboratory, which eliminate the low precision of immune assay in lower level of concentration.

Materials and Methods

MATERIALS AND METHODS

Study design: Prospective study.

Inclusion criteria:

All end stage renal disease patient who underwent renal transplantation between June 2012 and June 2013 in the department of nephrology, Rajiv Gandhi government general hospital were included.

Exclusion criteria:

Patients who had Graft dysfunction due to surgical issues, who underwent graft nephrectomy, who expired were excluded.

Eligible patients were enrolled. Their demographic profile such as age, sex, type of native kidney disease, type of donor whether live related or deceased, age and sex of donor, type of relation in case live related were collected. In immediate post operative period if the patient have raising creatinine, complete blood count, peripheral smear study, platelet count, serum lactic dehydrogenase, urine analysis, serum electrolytes, liver function test, urine and blood culture sensitivity were done. USG KUB, Renal Doppler and necessary investigations were done in order to rule out surgery related complication.

Whole blood cyclosporine/tacrolimus trough(C_O) level was assayed twelve hour after previous dose If the renal dysfunction does not

due to surgical complication and patient showed clinical feature of Calcineurin toxicity such as tremor, paresthesia, hypertension(worsening hypertension in need of more drugs and new onset hypertension), paresthesia, gum hypertrophy, hypertrichosis, sodium, potassium, cholesterol were done.

In this study cyclosporine trough level was assayed by enzyme linked microparticle immune assay(EMIA) and tacrolimus trough level was assayed by chemiluscent enzyme linked immune assay(CLEIA).

As per our department protocol for those receive induction treatment cyclosporine level was considered in therapeutic range if it was 200-250ng/ml at 0-1month, 100-200 ng/ml at 2-6 months, and around 100 ng/ml after 6months. For tacrolimus, the level was considered in therapeutic range if it was around 8 ng/ml at 0-1 month, 5-6 ng/ml at 3-6months, 3-5 ng/ml after 6months. For those didn't receive induction, cyclosporine level was considered in therapeutic range if it was 200-250ng/ml at 0-1month, 150-200ng/ml at 2-6 months, and around 100-150 ng/ml after 6months. For tacrolimus, the level was considered in therapeutic range if it was around 8-10ng/ml at 0-1 month, 7-8ng/ml at 3-6months, around 5ng/ml after 6months

Results and Analysis

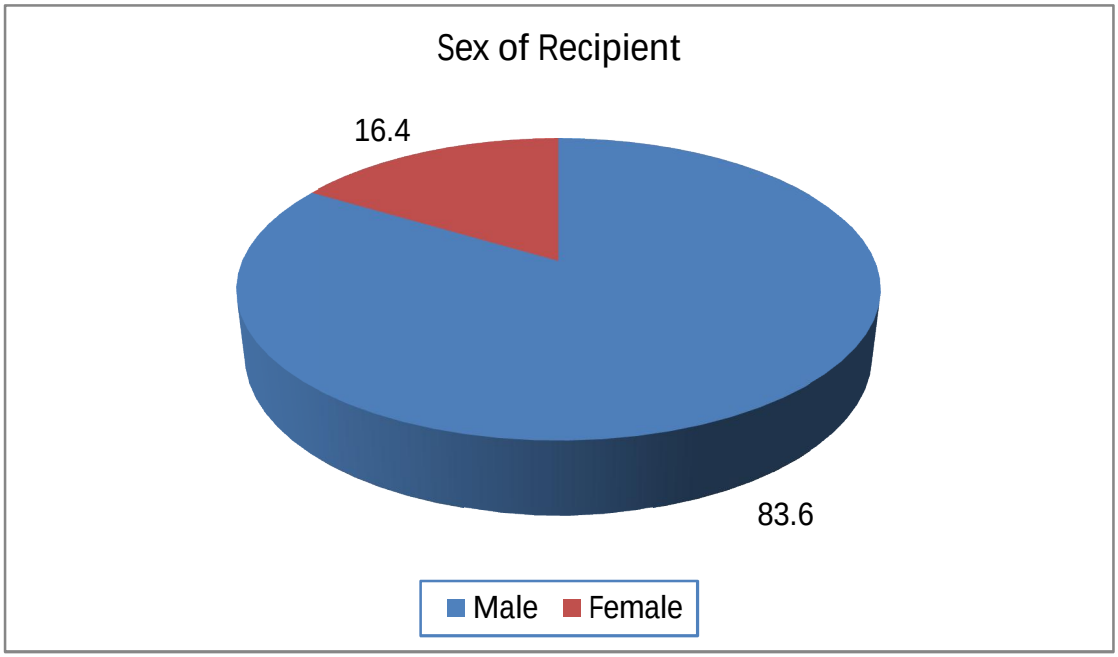
RESULTS

This study was conducted in our department among End Stage Renal Disease patients who underwent Renal Transplantation from June 2012 to June 2013. A total of sixty one patients were included out of seventy five. Of which males were 83.6% (51) and females were 16.4% (10), (Table 1).

Table 1

Recipient sex

Sex	No	%
Male	51	83.6
Female	10	16.4

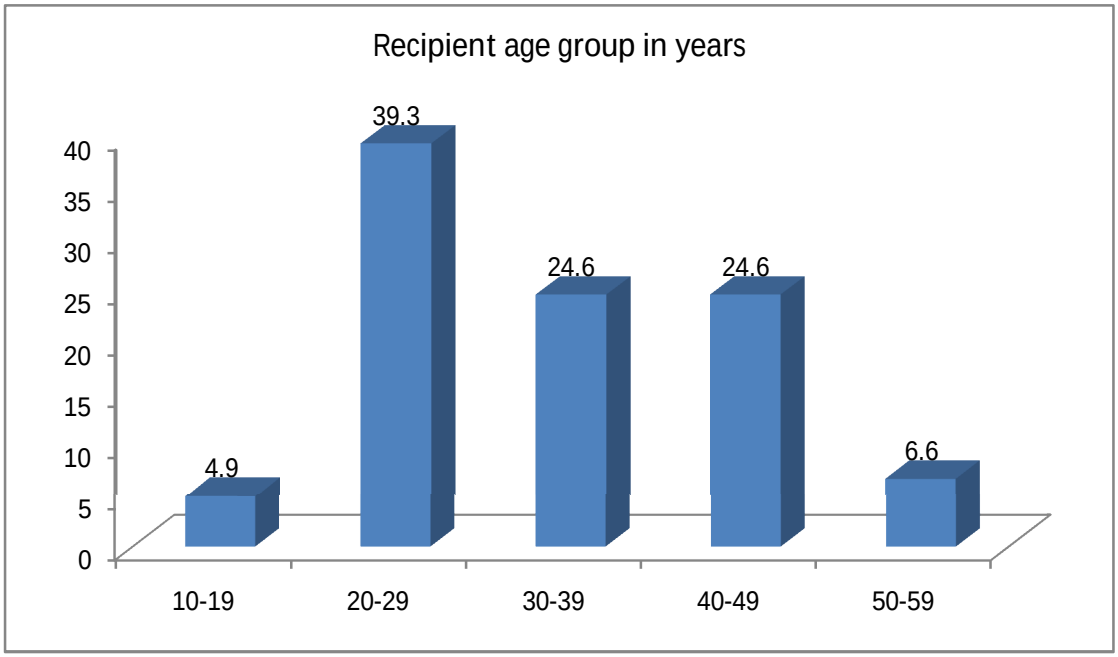


Among Recipients majority of them were in 3rd decade 39.3% (24), followed by equal proportion in 4th 24.6% (15) and 5th decade 24.6% (15), (Table 2). Mean age was 31.45(range: 17-56years).

Table 2

Recipient age group in years

Age group	No	%
10-19	3	4.9
20-29	24	39.3
30-39	15	24.6
40-49	15	24.6
50-59	4	6.6



70.5% patients were live related donor recipients and 29.5% were deceased donor recipients. (Table 3).

Table 3

Type of Donor

Type of donor	No	%
Live donor	43	70.5
Deceased donor	18	29.5

Among live related donor males were 16.7% (7) and females were 83.3% (36) (Table 4).

Table 4

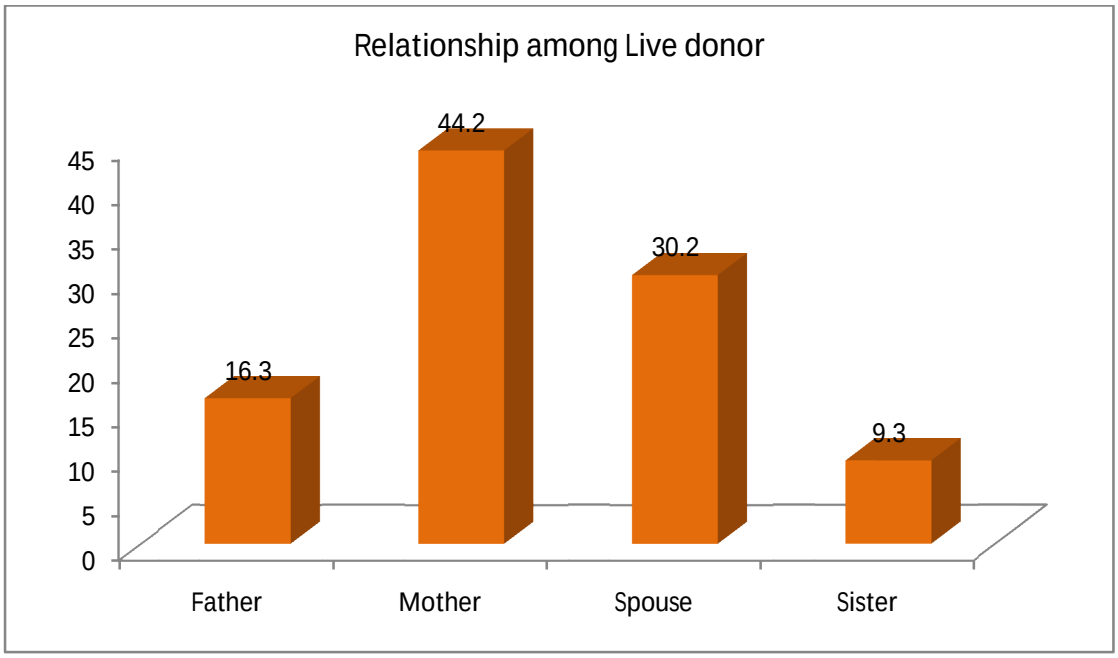
Sex Ratio of Live Donor

Sex	No	%
Male	7	16.7
Female	36	83.3

Of which mothers were 44.2% (19), followed by spouse 30.2% (13), fathers 16.3% (7) and sisters 9.3%(4), (Table 5).

Table 5 : Relationship among Live donor

Relation	No	%
Father	7	16.3
Mother	19	44.2
Spouse	13	30.2
Sister	4	9.3

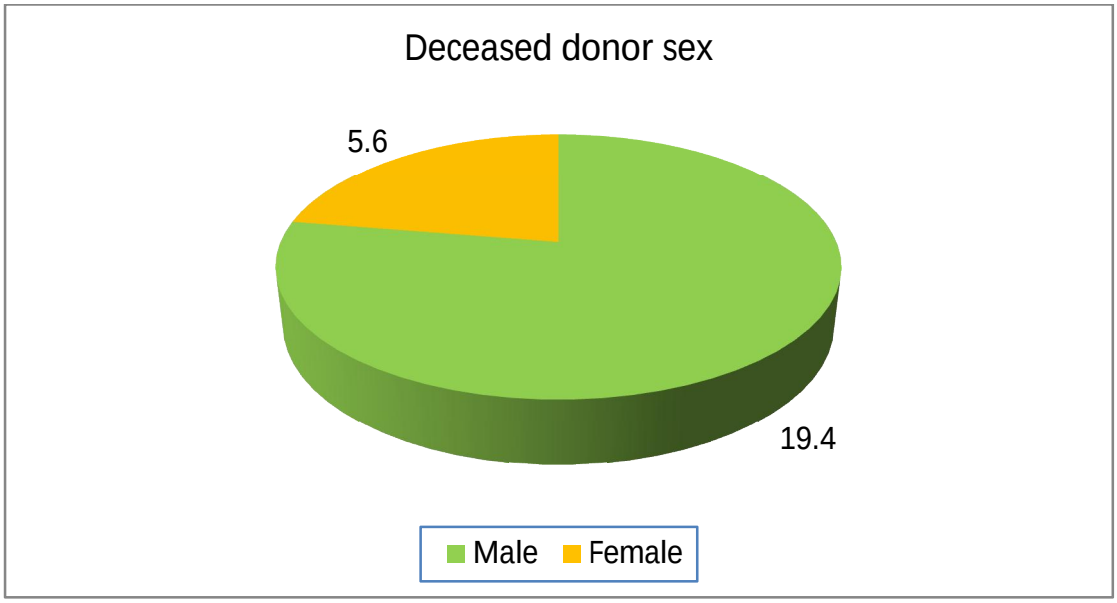


Among deceased donor males were 19.4% (17) and females were 5.6% (1), (Table 6).

Table 6

Deceased donor sex

Sex	No	%
Male	17	19.4
Female	1	5.6



After renal transplantation recipients were treated with immunosuppressive agents [three drugs : calcineurine Inhibitors (cyclosporine / Tacrolinus) + mycophenolate Mofetile / Azathioprine + Steroids] as per our department protocol. Induction treatment was given as per our department protocol [rabbit Anti Thymocyte Globulin / Interleukin – 2 receptor Antagonist) for high risk recipients such as those received organ from deceased donor, spouse donor and second transplant). These patients were followed up for 0-18 months (mean 12.5

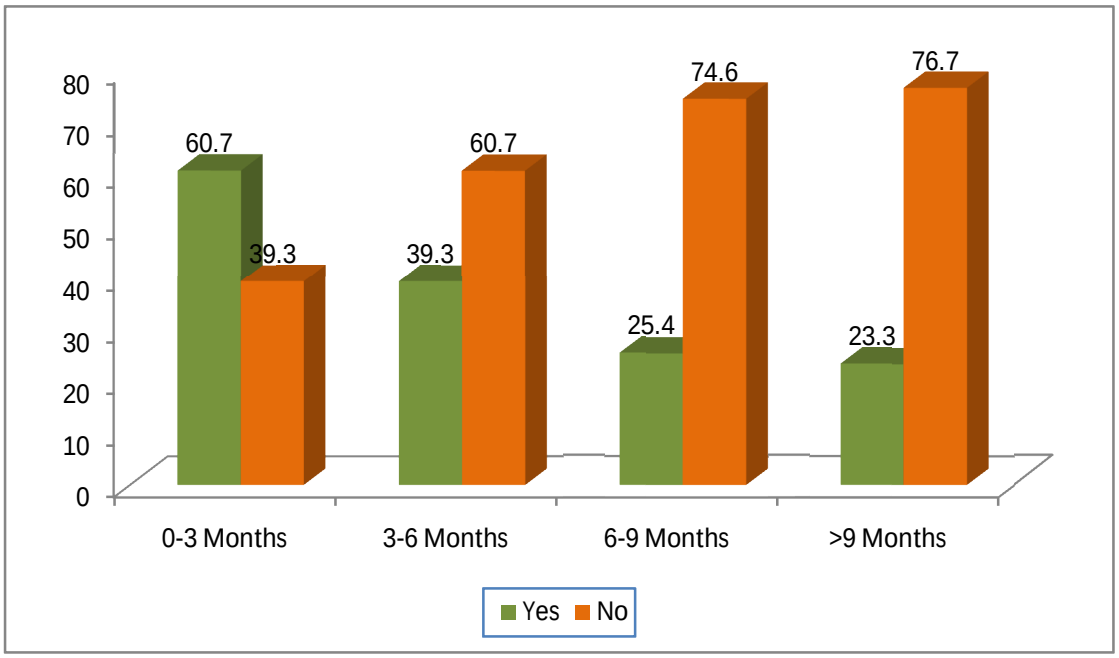
months) for calcineurin inhibitor toxicity. Observed toxic features were grouped into 0-3, 3-6, 6-9 and more than 9 months of post transplant age.

Follow up revealed that toxicity of calcineurin inhibitors were clinically present in 60.7% (37) in 0-3, 39.3% (24) in 3-6, 25.4%(15) in 6-9 months and 23.3%(10) in more than 9 months(Table 7).

Table 7

Clinical CNI toxicity

Clinical toxicity	0-3 months		3-6 months		6-9months		>9months	
	n	%	n	%	n	%	n	%
Yes	37	60.7	24	39.3	15	25.4	10	23.3
No	24	39.3	37	60.7	44	74.6	33	76.7



Among them, further toxicity profile was evaluated and grouped into 0-3, 3-6, 6-9 and >9 months. Evaluated toxicity profile were tremor,

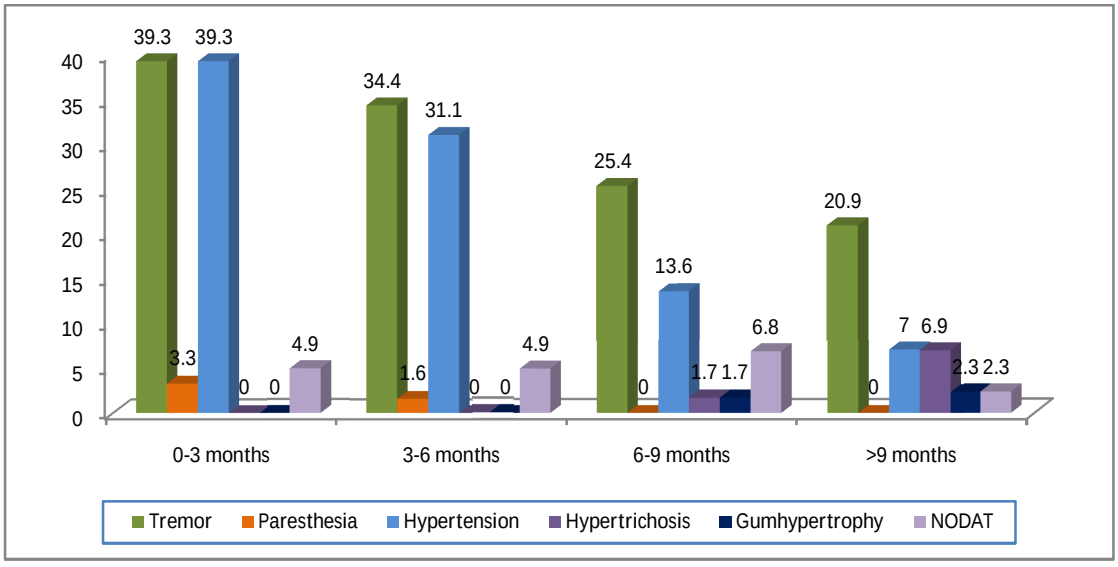
paresthesia, hypertension(new onset /worsening), hypertrichosis, gum hypertrophy and NODAT(based on ADA guidelines) (Table 8).

Table 8

CNI Toxicity Profile

		0-3 months		3-6 months		6-9months		>9months	
		n	%	n	%	n	%	n	%
Tremor	Yes	24	39.3	21	34.4	15	25.4	9	20.9
	No	37	60.7	40	65.6	44	74.6	34	79.1
Paresthesia	Yes	2	3.3	1	1.6	0	0	0	0
	No	59	96.7	60	98.4	59	100	43	100
Hypertension	Yes	24	39.3	19	31.1	8	13.6	3	7
	No	37	60.7	42	68.9	51	86.4	40	93
Hypertrichosis	Yes	0	0	0	0	1	1.7	3	6.9
	No	61	100	61	100	60	98.3	40	93.1
Gumhypertrophy	Yes	0	0	0	0	1	1.7	1	2.3
	No	61	100	61	100	60	98.3	40	97.7
NODAT	Yes	3	4.9	3	4.9	4	6.8	1	2.3
	No	58	95.1	58	95.1	55	93.2	42	97.7

Percentage of patients with CNI toxicity



Tremor was present in 39.3% (24) in 0-3 months, 34.4% (21) in 3-6 months, 25.4% (15) in 6-9 months and 20.9% (9) in more than 9 months. Hypertension was present in 39.3% (24) in 0-3 months, 31.1%

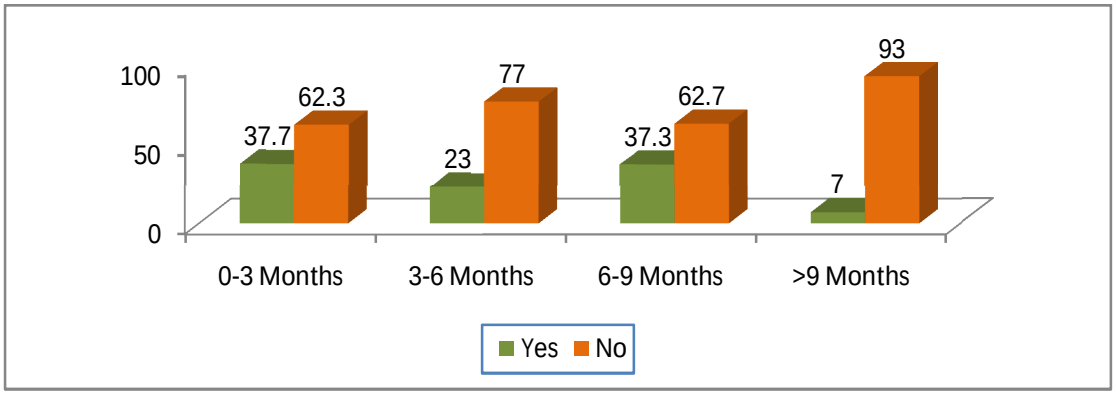
(19) in 3-6 months, 13.6% (6) in 6-9 months and 7% (3) in more than 9 months. Hypertrichosis and gum hypertrophy were present in few patients after 6 months of transplant. NODAT was present in 4.9% (93) in 0-3 months and 3-6 months, 6.8% (4) in 6-9 months and 2.3% (1) in more than 9 months.

During follow up improvement in graft dysfunction following tapering with calcineurin inhibitor was presumed to be due to calcineurin inhibitor toxicity after excluding rejection. Table 9 showed that graft dysfunction due to calcineurin inhibitor toxicity.

Table 9

Graft dysfunction

	0-3 months		3-6 months		6-9 months		>9 months	
	n	%	n	%	n	%	n	%
Yes	23	37.7	14	23	22	37.3	3	7
No	38	62.3	47	77	37	62.7	40	93



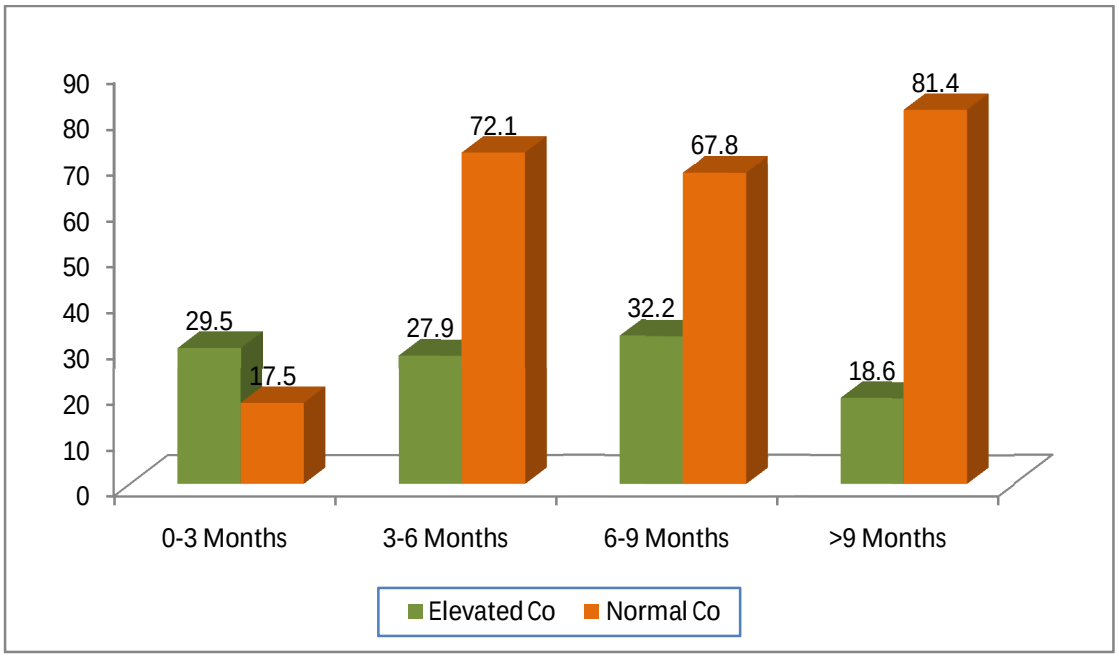
Graft dysfunction was in 37.7% (23) in 0-3 months, 23% (14) in 3-6 months, 37.3% (22) in 6-9 months, and 7% (3) in more than 9 months.

Whole blood trough(Co) level was done. Which shown in Table 10.

Table 10

Trough (Co) level

	0-3 months		3-6 months		6-9 months		>9 months	
	n	%	n	%	n	%	n	%
Elevated C_O	18	29.5	17	27.9	19	32.2	8	18.6
Normal Co	43	17.5	44	72.1	40	67.8	35	81.4



Elevated trough level was seen in 29.5% (18) in 0-3 months, 27.9% (17) in 3-6 months, 32.2% (19) in 6-9 months and 18.6% (8) in more than 9 months.

Biopsy and histopathological examination was done only in small number of patients because of its invasiveness and procedure related

complication, patient willingness and improvement with tapering of drugs. Biopsy features were shown in Table 11.

Table 11

Histopathological features of CNI toxicity

	0-3 months		3-6 months		6-9 months		>9 months	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Iso.vacuolization	6	9.8	5	8	2	3.4	0	0
Med. Hyalinosis	2	3.3	1	1.6	0	0	0	0
TMA	1	0	0	0	0	0	0	0
Glomerulosclerosis	0	0	0	0	0	0	0	0
Intertial fibrosis	0	0	1	0	0	0	0	0
Tubular atrophy	0	0	1	0	0	0	0	0
CNI Toxicity	6	9.8	5	8.2	2	3.4	0	0

In 0-3 months Six patients were found to have histopathological features of CNI toxicity. Isometric vacuolization was found in all biopsies, medullary hyalinosis and thrombotic microangiopathy were seen in two and one of those biopsies. In 3-6 months 5 patients shown histopathological evidence of CNI toxicity of which isometric vacuolization was present in all five biopsies and medullary hylinosis present in one biopsy. In 6-9 months, 2 patients were shown evidence of histopathological toxicity, isometric vacuolization was present in both of them.

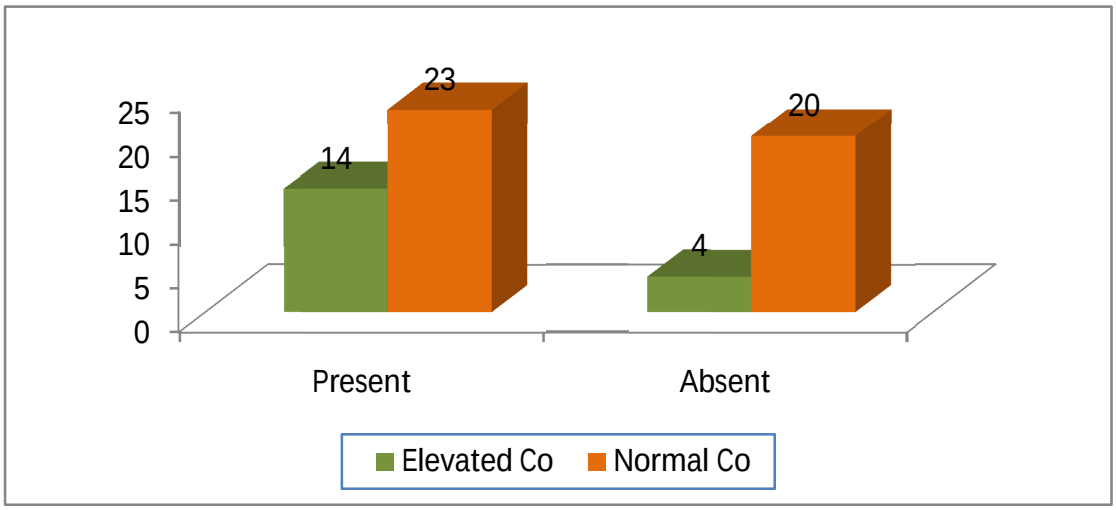
ANALYSIS

Statistical analyses were done by SPSS 20.6 software. Analysis was done in each post transplant age group. Factors analyzed were trough (Co) level (elevated trough (Co) level / normal trough (Co) level) versus clinical toxicity, tremor, paresthesia, hypertension, NODAT, graft dysfunction and histopathological toxicity. Hypertrichosis and gum hypertrophy were not analyzed because of its lower frequency in this study groups.

ANALYSIS AT 0-3 MONTHS

Clinical Toxicity vs Trough Level (0-3 months)

		Elevated C_O	Normal C_O	P
Clinical toxicity	Present	14	23	0.077
	Absent	4	20	



Analysis revealed that no significant correlation between the clinical toxicity and trough (Co) level.

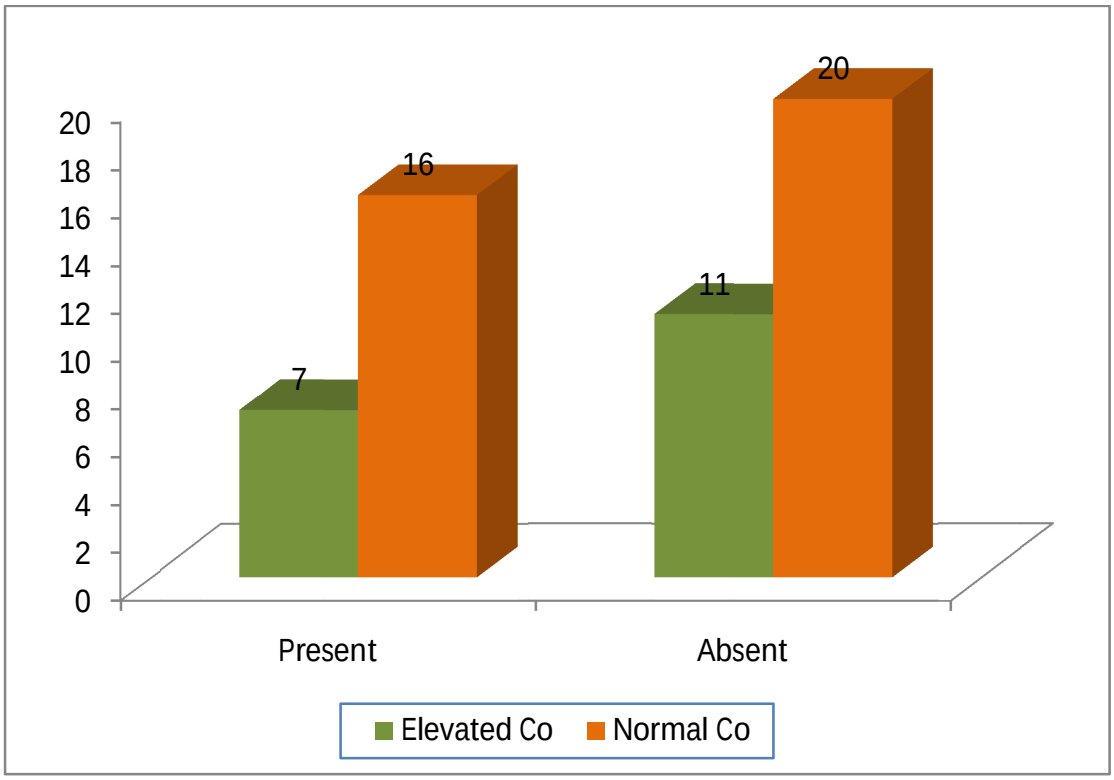
Clinical features versus Trough (Co) level (0-3 months)

		Elevated C_O	**Normal C_O**	**P**
Tremor	Present	10	14	0.094
	Absent	8	29	
Paresthesia	Present	1	1	0.518
	Absent	17	42	
Hypertension	Present	6	18	0.534
	Absent	12	25	
NODAT	Present	2	1	0.148
	Absent	16	42	

There is no significant correlation between tremor, paresthesia, hypertension, NODAT and trough (Co) level.

Graft Dysfunction Vs Trough (Co) level (0-3 months)

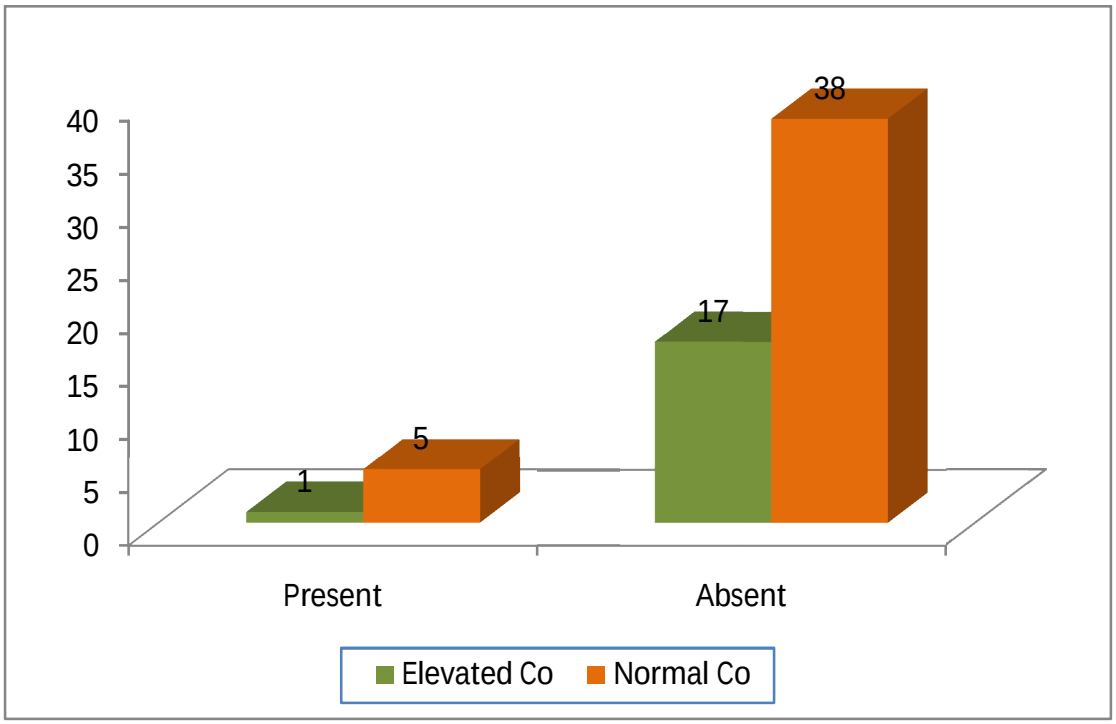
		Elevated C_O	Normal C_O	P
Graft dysfunction	Present	7	16	0.902
	Absent	11	27	



Analysis revealed that no significant correlation between the graft dysfunction and trough (Co) level.

Histopathological Toxicity Vs Trough (Co) level (0-3 months)

		Elevated C_O	Normal C_O	P
Histopathological toxicity	Present	1	5	0.468
	Absent	17	38	

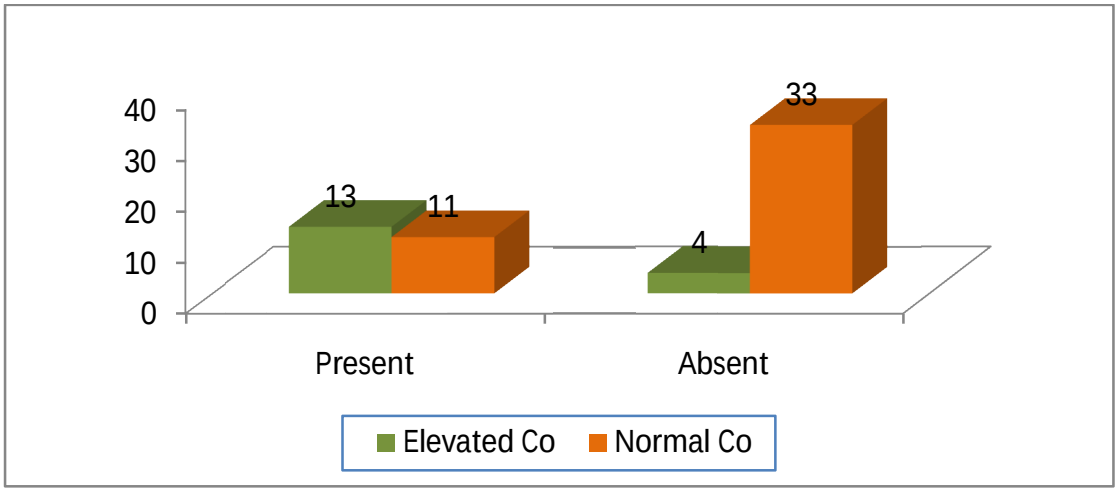


Analysis revealed that no significant correlation between the histopathological toxicity and trough (Co) level.

ANALYSIS AT 3-6 MONTHS

Clinical toxicity vs Trough (Co) level (3-6 months)

		Elevated C_O	Normal C_O	P
Clinical toxicity	Present	13	11	0.001
	Absent	4	33	



Analysis revealed that there was significant correlation between the clinical toxicity and trough (Co) level.

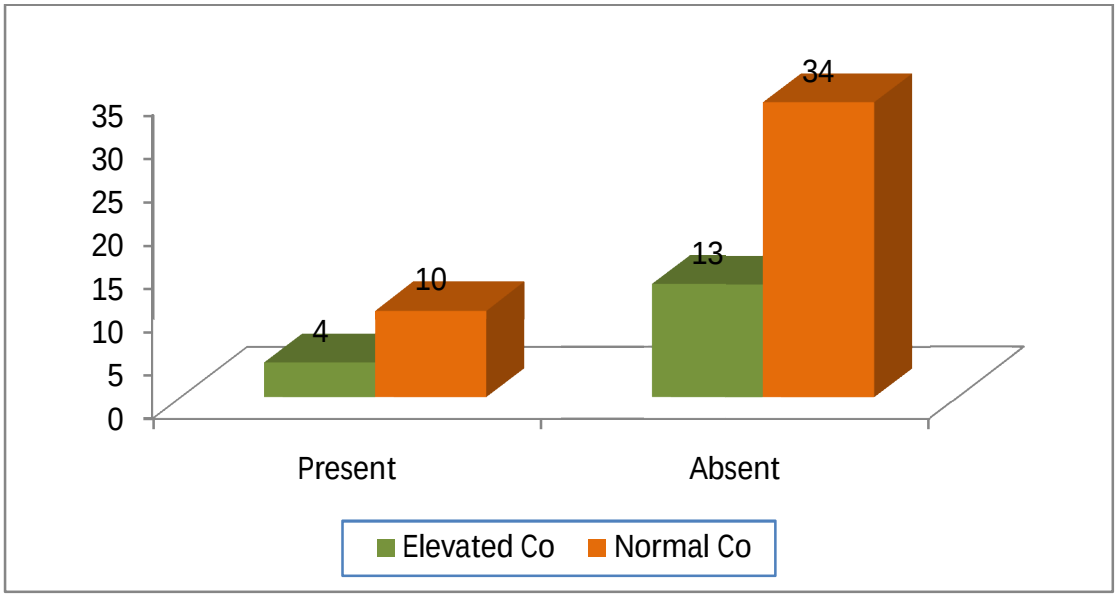
Clinical features Vs Trough (Co) level (3-6 months)

		Elevated C_O	Normal C_O	P
Tremor	Present	13	8	0.001
	Absent	4	36	
Paresthesia	Present	0	1	0.531
	Absent	17	43	
Hypertension	Present	7	12	0.295
	Absent	10	32	
NODAT	Present	1	2	0.829
	Absent	16	42	

Analysis revealed that there was significant correlation between tremor and elevated trough level. No significant correlation between paresthesia, hypertension, NODAT and elevated trough(Co) level.

Graft Dysfunction Vs Trough (Co) level (3-6 months)

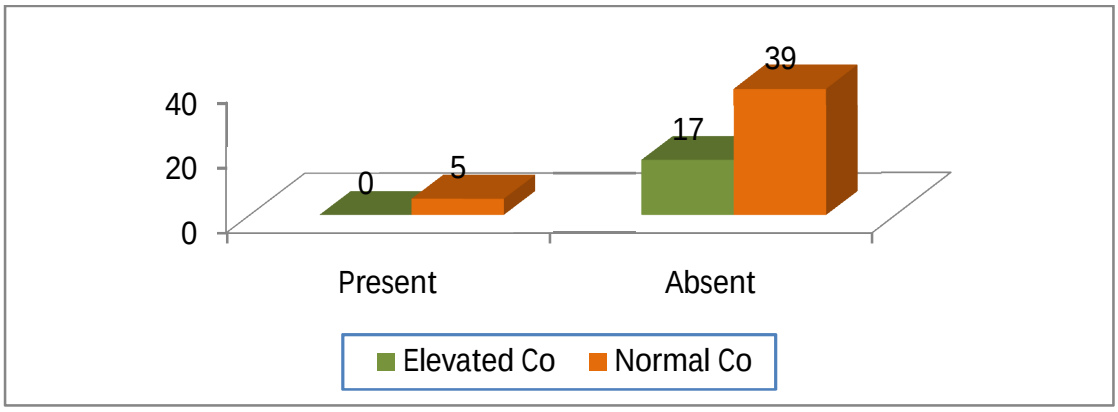
		Elevated C_O	**Normal C_O**	P
Graft dysfunction	Present	4	10	0.947
	Absent	13	34	



Analysis revealed that no significant correlation between the graft dysfunction and trough (Co) level.

Histopathological Toxicity Vs Trough (Co) level (3-6 months)

		Elevated C_O	**Normal C_O**	**P**
Histopathological toxicity	Present	0	5	0.147
	Absent	17	39	

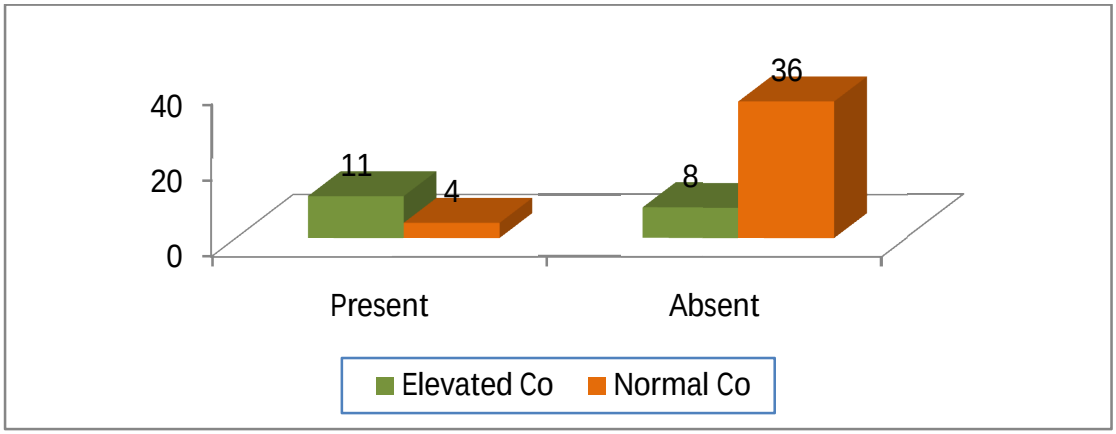


Analysis revealed that no significant correlation between the histopathological toxicity and trough (Co) level.

ANALYSIS AT 6-9 MONTHS

Clinical Toxicity Vs Trough (Co) level (6-9 months)

		Elevated C_O	**Normal C_O**	**P**
Clinical toxicity	Present	11	4	0.001
	Absent	8	36	



Analysis revealed that there was significant correlation between the clinical toxicity and trough (Co) level.

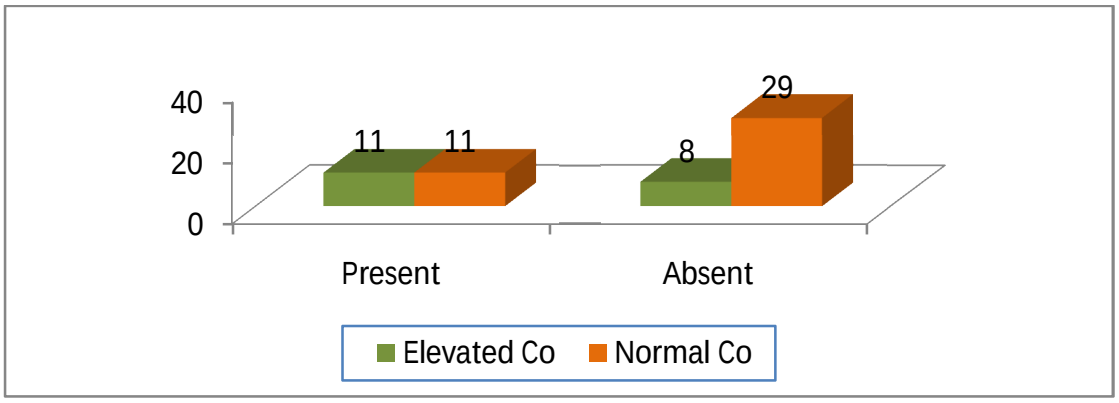
Clinical Features Vs Trough (Co) level (6-9 months)

		Elevated C_O	Normal C_O	P
Tremor	Present	12	3	0.001
	Absent	7	37	
Paresthesia	Present	0	0	
	Absent	0	0	
Hypertension	Present	6	2	0.005
	Absent	13	38	
NODAT	Present	2	2	0.430
	Absent	17	38	

There was significant correlation between tremor and trough level. No significant correlation between paresthesia, hypertension, NODAT and trough level.

Graft dysfunction Vs Trough (Co) level (6-9 months)

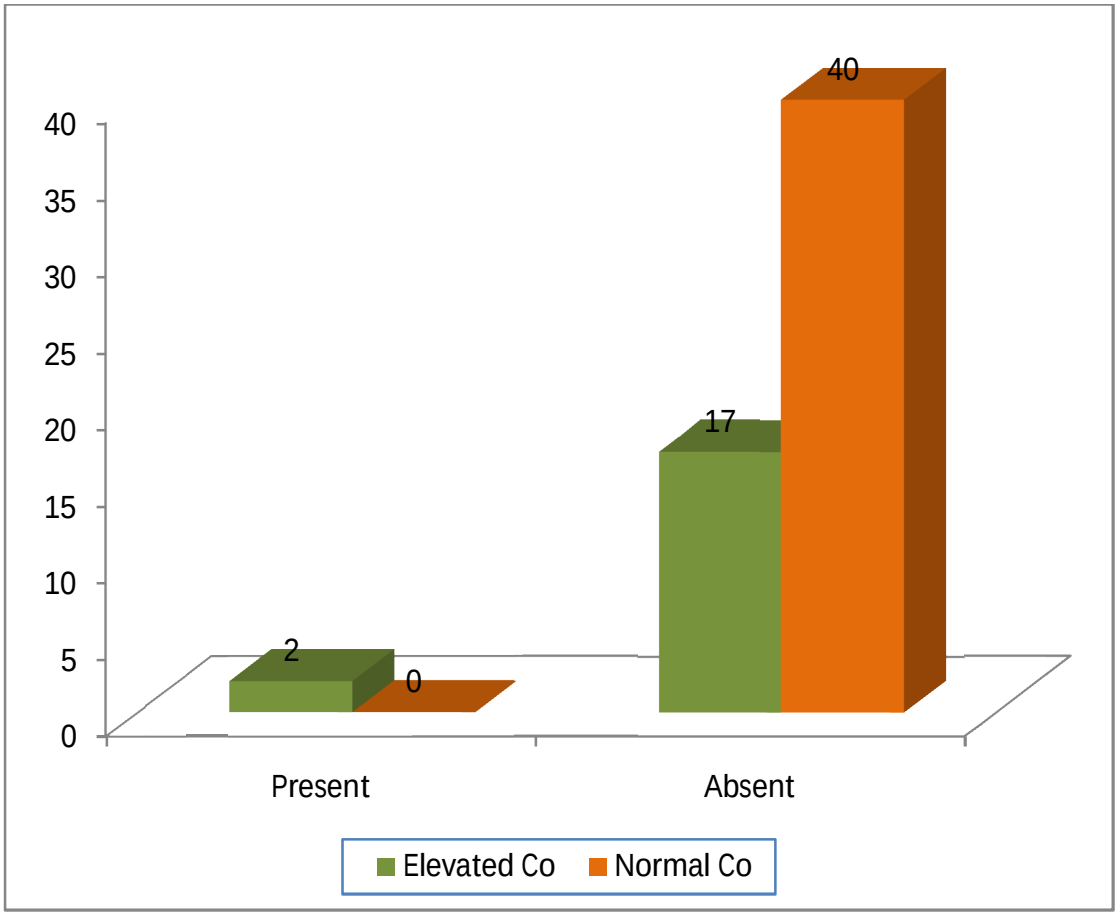
		Elevated C_O	Normal C_O	P
Graft dysfunction	Present	11	11	0.024
	Absent	8	29	



Analysis revealed that no significant correlation between the Graft dysfunction and trough (Co) level.

Histopathological toxicity Vs Trough level (6-9 months)

		Elevated C_O	Normal C_O	P
HPE	Present	2	0	0.37
	Absent	17	40	

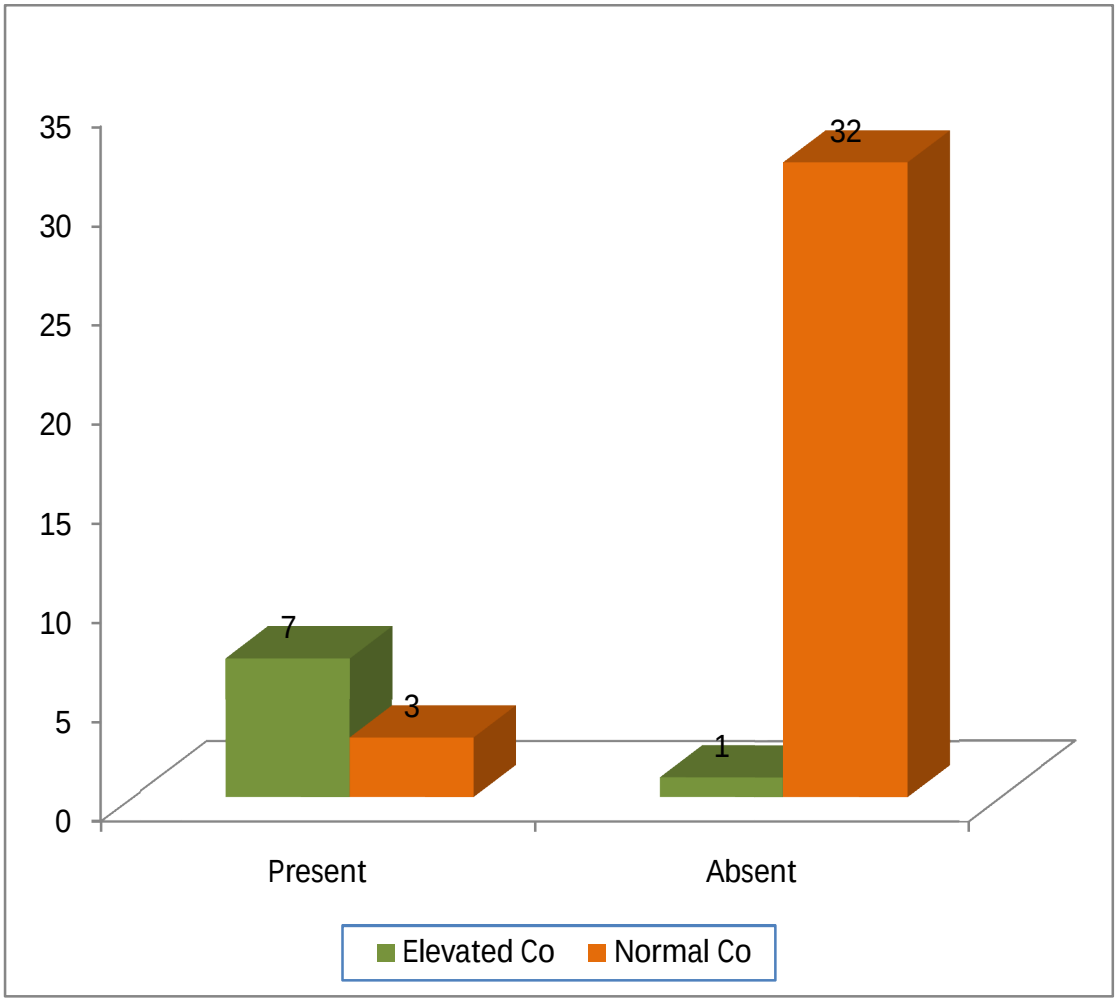


Analysis revealed that no significant correlation between the histopathological toxicity and trough (Co) level.

ANALYSIS AT >9 MONTHS

Clinical Toxicity Vs Trough (Co) level (>9 months)

		Elevated C_O	Normal C_O	P
Clinical toxicity	Present	7	3	22.72
	Absent	1	32	



Analysis revealed that no significant correlation between the Clinical toxicity and trough (Co) level.

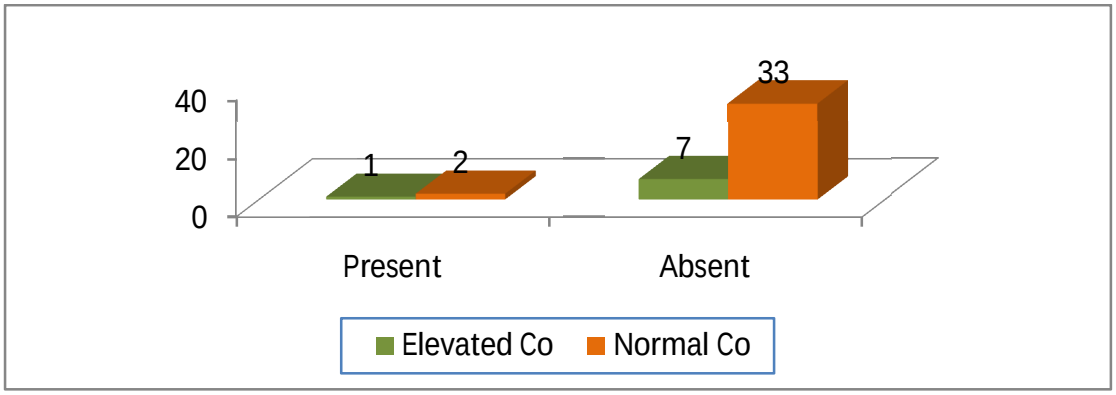
Clinical Features Vs Trough (Co) level (>9 months)

		Elevated C_O	Normal C_O	P
Tremor	Present	6	3	17.36
	Absent	2	32	
Paresthesia	Present	0	0	0
	Absent	0	0	
Hypertension	Present	2	1	4.91
	Absent	6	34	
NODAT	Present	1	0	4.47
	Absent	7	35	

There was no significant correlation between tremor, paresthesia, hypertension, NODAT and trough level.

Graft Dysfunction Vs Trough (Co) level (>9 months)

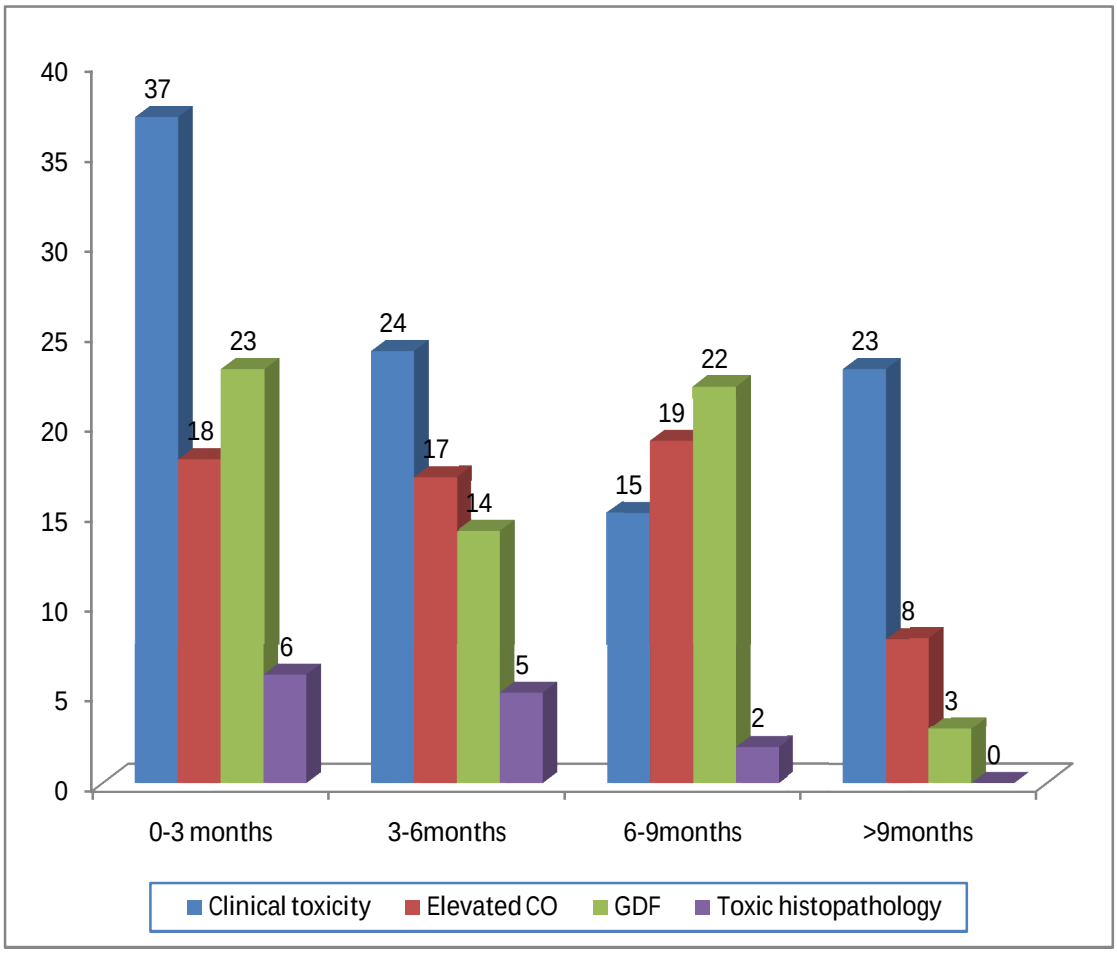
		Elevated C_O	Normal C_O	P
Graft dysfunction	Present	1	2	0.462
	Absent	7	33	



Analysis revealed that no significant correlation between the Graft dysfunction and trough (Co) level.

The Correlation between clinical, trough (Co) level, graft function and histopathological toxicity

	Clinical toxicity	Elevated C_O	GDF	Histopathological Toxicity	P
0-3 months	37	18	23	6	3.28
3-6months	24	17	14	5	3.81
6-9months	15	19	22	2	2.86
>9months	23	8	3	0	1.66



There was no significant correlation between clinical toxicity, elevated trough level, graft dysfunction, histopathological toxicity at 3-6, 6-9 and > 9 months.

TACROLIMUS VS CYCLOSPORINE

0-3MONTHS

		Tacrolimus	Cyclosporine	P
Tremor	Present	8	16	0.046
	Absent	22	15	
Paresthesia	Present	1	1	0.981
	Absent	29	30	
Hypertension	Present	13	11	0.530
	Absent	17	20	
NODAT	Present	3	0	0.071
	Absent	27	31	
Clinical toxicity	Present	18	19	0.918
	Absent	12	12	
Graft dysfunction	Present	9	14	0.222
	Absent	21	17	
Ttoxicity on HPE	Present	2	4	0.414
	Absent	28	27	

There was significant correlation between presence of tremor and Tacrolimus at 0-3 months. But there was no significant correlation between tacrolimus and cyclosporine in manifestation of paresthesia, hypertension, NODAT, overall clinical toxicity, graft dysfunction and histopathological toxicity.

TACROLIMUS VS CYCLOSPORINE

3-6 MONTHS

		Tacrolimus	Cyclosporine	P
Tremor	Present	10	11	0.860
	Absent	20	20	
Paresthesia	Present	1	0	0.305
	Absent	29	31	
Hypertension	Present	10	9	0.717
	Absent	20	22	
NODAT	Present	1	2	0.573
	Absent	29	29	
Clinical toxicity	Present	12	12	0.918
	Absent	18	19	
Graft dysfunction	Present	8	6	0.497
	Absent	22	25	
Toxicity on HPE	Present	1	4	0.173
	Absent	29	27	

There was no significant correlation between tacrolimus and cyclosporine in manifestation of tremor, paresthesia, hypertension, NODAT, overall clinical toxicity, graft dysfunction and histopathological toxicity.

TACROLIMUS VS CYCLOSPORINE

6-9 MONTHS

		Tacrolimus	Cyclosporine	P
Tremor	Present	6	9	0.412
	Absent	23	21	
Paresthesia	Present	0	0	0
	Absent	29	30	
Hypertension	Present	3	5	0.478
	Absent	26	25	
NODAT	Present	3	1	0.284
	Absent	26	29	
Clinical toxicity	Present	7	8	0.824
	Absent	22	22	
Graft dysfunction	Present	7	15	0.404
	Absent	22	15	
Toxicity on HPE	Present	0	2	0.157
	Absent	29	28	

There was no significant correlation between tacrolimus and cyclosporine in manifestation of tremor, paresthesia, hypertension, NODAT, overall clinical toxicity, graft dysfunction and histopathological toxicity

TACROLIMUS VS CYCLOSPORINE

>9 MONTHS

		Tacrolimus	Cyclosporine	P
Tremor	Present	6	3	0.061
	Absent	11	23	
Paresthesia	Present	0	0	0
	Absent	17	26	
Hypertension	Present	2	1	0.319
	Absent	15	25	
NODAT	Present	1	0	0.211
	Absent	16	26	
Clinical toxicity	Present	7	3	0.204
	Absent	10	23	
Graft dysfunction	Present	0	3	0.146
	Absent	17	23	

There was no significant correlation between tacrolimus and cyclosporine in manifestation of tremor, paresthesia, hypertension, NODAT, overall clinical toxicity and graft dysfunction.

Discussion

DISCUSSION

In our study total of sixty one renal allograft recipients who underwent renal allograft transplantation from June 2012 to June 2013 at our centre were included. Followed up for the period of 0-18 month (median of 12.5 months) for calcineurin inhibitor toxicity. Out of sixty one 83.6% (51) were male and 16.4 %(10) were female, majority of them were in third decade of life. Among donors, live versus deceased donor was 70.5% (43) and 29.5% (18). Majority of the live donors were mother 44.2 %(19) followed by spouse 30.2% (13).

Prevalence of clinical calcineurin inhibitor toxicity was 60.7%(37), 39.3%(24), 25.4%(15) and 23.3%(10) at 0-3, 3-6, 6-9, and >9 months respect tively. Among clinical features tremor and hypertension were present in majority of the recipients [tremor: 39.3%(24), 34.4% (21) , 25.4% (15) and 20.9% (9); hypertension: 39.3% (24), 31.1% (19) , 13.6% (6) and 7% (3) at 0-3, 3-6, 6-9 and >9 months respectively]. NODAT was present in 4.9% (93) in 0-3 & 3-6 months, 6.8% (4) in 6-9 months and 2.3% (1) in more than 9 months. Graft dysfunction was in 37.7% (23), 23% (14) , 37.3% (22), and 7% (3) at 0-3, 3-6, 6-9 month and thereafter. Elevated trough level was seen in 29.5% (18) , 27.9% (17), 32.2% (19) and 18.6% (8) at 0-3, 3-6, 6-9 month and thereafter.

Neeraja kambham[20] et al shown that incidence of hypertension was 24% at 3 and 6 months and 18% at 12 months.

Jose M morale[21] et al shown that prevalence of hypertension was 60-85% in patients on calcineurin inhibitors. More than fifty percent of well functioning graft showed arterial hypertension.

Vincenti[22] et al shown that prevalence of new onset diabetes after trans plantation was 15%.

Zibiti[23] et al shown that after a mean transplantation time of three months, 14/92 (15.2%) transplanted patients developed NODAT in his study of 92patients.

Sitagourishankar[24]et al shown that prevalence of new onset diabetes was 6.7% at 6 months, 7.0% at 12 months and 8.0% at 3 years post transplant (study on 386 adult kidney transplant recipient). Incidence of new onset diabetes in our study coincides with him.

In our study trough level was significantly correlated with tremor and clinical toxicity at 3-6 and 6-9 month($P<0.001$). Trough level doesn't correlate with tremor, hypertension, NODAT, graft dysfunction. In 0-3 and more than nine months trough level didn't correlate with clinical toxicity, graft dysfunction and histopathological toxicity.

Maryam hami et al shown that in his study among 50 kidney transplant recipients from one week to six months of post transplant age shown that no significant relationships neither between serum cyclosporine levels and graft function nor between cyclosporine dose and C_O, except at second week and sixth month after transplantation. After fourth month, none the patients with low Co levels had tremor, but 24.7% of the patients with Co levels within therapeutic level and 66.7% with Co levels higher than the therapeutic level had tremor, no significant relation between Co level and blood glucose and blood pressure.

In our study 6, 5 and 2 patients at 0-3months, 3-6 months and 6-9 months showed evidence of calcineurin inhibitor toxicity in renal biopsy. Isometric vacuolization was seen in all thirteen biopsies, medullary hyalinosis was seen in three of thirteen biopsies and thrombotic microangiopathy in one biopsy.

Alok Sharma[25] et al from AIIMS shown that in his 140 protocol biopsy study among kidney transplant recipients, histopathological evidence of toxicity was present in 10.3%, 13.3%, and 5.4% at one month, sixth month and twelve month. Among histological features arterial hyalinosis was significantly correlated feature of CNI toxicity.

Higher number of isometric vacuolization in our study might be due to acute CNI toxicity.

Neeraja kampham et al shown that the incidence of CNI toxicity was higher in protocol biopsy over clinically indicated biopsies 41.5% vs 22%.

In our study analysis of trough level vs hypertension, tremor, new onset diabetes, overall clinical toxicity, graft dysfunction and histopathological toxicity were not correlated significantly at 0-3, 3-6, 6-9 and more than 9 months except trough level versus tremor and overall clinical toxicity at 3-6 and 6-9 months.

In our study there was no significant correlation between clinical toxicity, trough level, graft dysfunction and histopathological correlation at 0-3, 3-6, 6-9 and >9 months.

Karel karejci[26] et al also shown that there was no significant correlation between graft dysfunction, elevated trough level and histopathological toxic features at 3 weeks, 3months and 1 year.

In our study tacrolimus and cyclosporine was compared. Statistical analysis shown that there was significant correlation between tremor and elevated trough level at 0-3 and 3-6 months. There was no significant correlation between trough level and hypertension, new onset diabetes, graft dysfunction and histopathological toxicity.

Martins[27] et al showed that in his study of tacrolimus vs cyclosporine in renal allograft recipient, tacrolimus patients showed better renal function; namely, creatinine was 1.15 +/- 0.27 versus 1.44 +/- 0.33 mg/dL (P =.029). Lipid and blood pressure values were not different between the 2 subgroups, the incidence of de novo diabetes mellitus was approximately 20% among patients using tacrolimus

Margreiter[28] et al in his comparative study of tacrolimus vs cyclosporine(micro emulsion) in 560 patients shown that the overall frequency of adverse events was similar in the two groups, though hypertension and hypercholesterolemia were more common in the cyclosporine group and tremor and hypomagnesaemia were more frequent in the tacrolimus group.

Angela C Webster[29] et al in his meta analysis of tacrolimus vs cyclosporine from 30 trials shown that at one year, tacrolimus treated patients had less acute rejection (RR = 0.69, 0.60 to 0.79) and less steroid resistant rejection (RR = 0.49, 0.37 to 0.64) but more diabetes mellitus requiring insulin (RR = 1.86, 1.11 to 3.09), tremor, headache. The relative excess of diabetes was increased with higher concentrations of tacrolimus (P = 0.003).

Conclusion

CONCLUSION

1. In our study a significant correlation between tremor, clinical toxicity and elevated trough (Co) level at 3-6 and 6-9 month ($P<0.001$) was observed.

3. There was no significant correlation between clinical toxicity, trough level, graft dysfunction and histopathological correlation at 0-3, 3-6, 6-9 and >9 months.

4. There was a significant correlation between tremor and elevated trough level of tacrolimus was observed at 0-3 and 3-6 months.

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Annexure

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Gandhi Mohan,
Postgraduate,
Department of Nephrology
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai-3.

Dear **Dr. Gandhi Mohan,**

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"A study on Clinical, Biochemical, Drug Trough Level and Histopathological Correlation of Calcineurin Inhibitor (CNI) Toxicity in Renal Allograft Recepient"** No.18122012.

The following members of Ethics Committee were present in the meeting held on 11.12.2012 conducted at Madras Medical College, Chennai-3.

1. Dr. G. Sivakumar, MS FICS FAIS	-- Chairperson
2. Prof. B. Kalaiselvi, MD Vice Principal, MMC, Ch-3	-- Member Secretary
3. Prof. Ramadevi, Director i/c, Instt. of Biochemistry, MMC, Ch-3	-- Member
4. Prof. P. Karkuzhali, MD for Dr. V. Ramamoorthy Prof. Instt. of Pathology, MMC, Ch-3	-- Member
5. Thiru. S. Govindasamy, BA, BL	-- Lawyer
6. Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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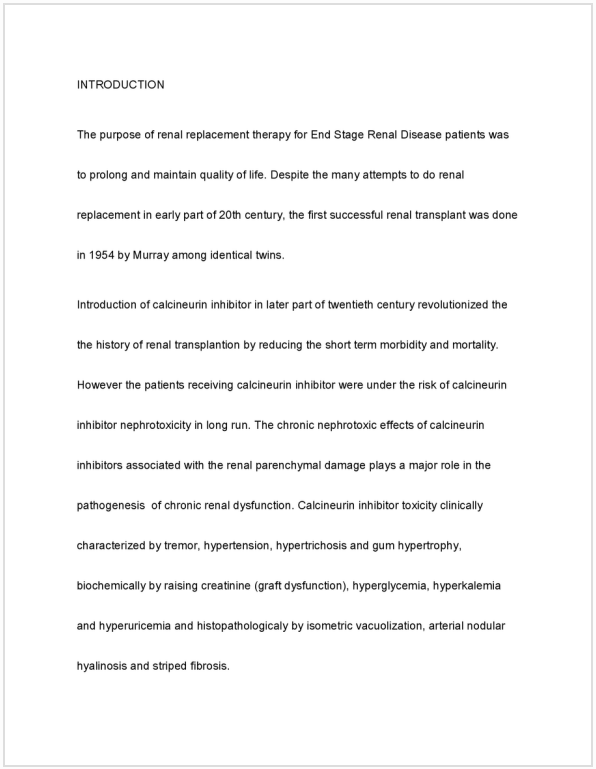
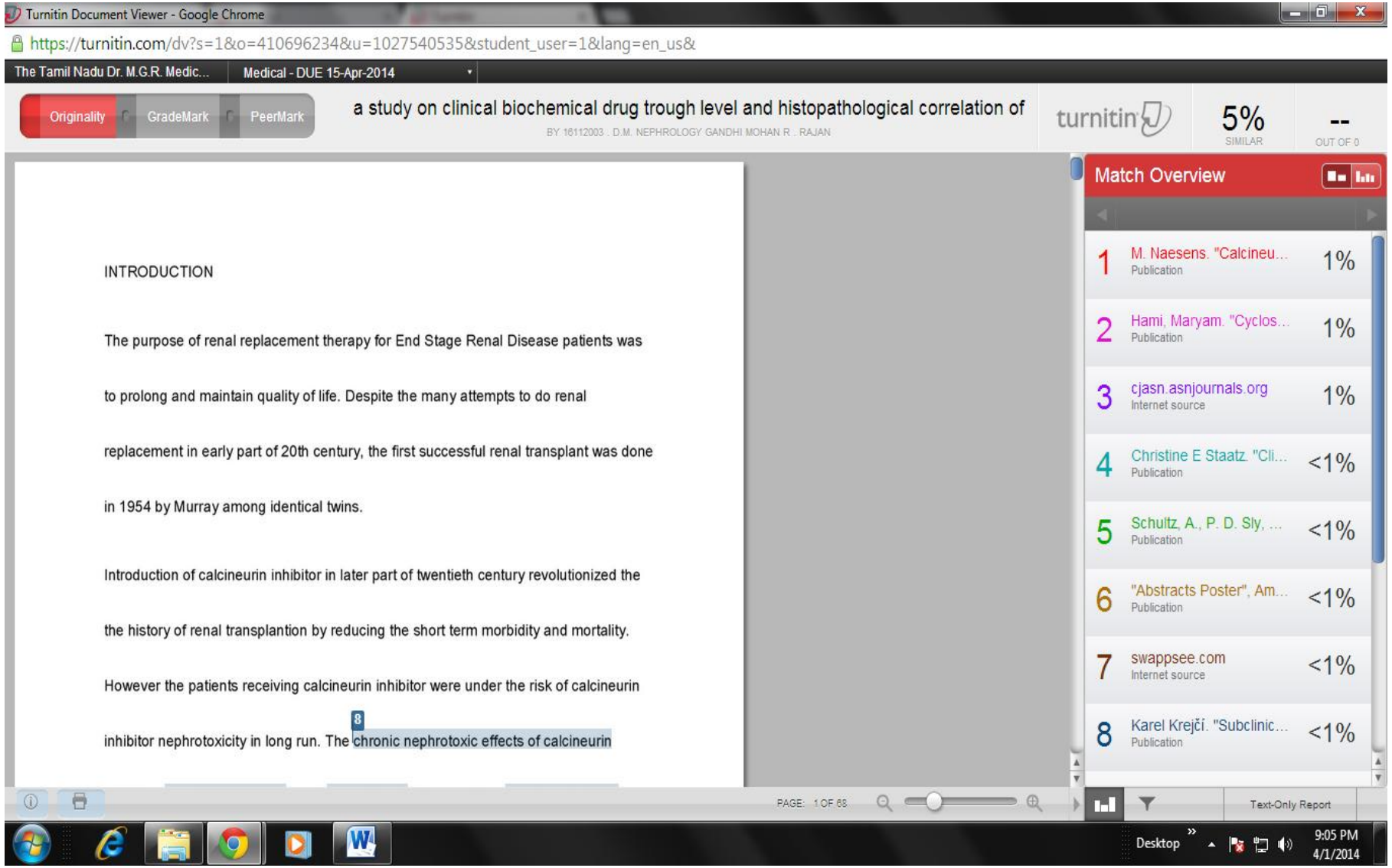


INTRODUCTION

The purpose of renal replacement therapy for End Stage Renal Disease patients was to prolong and maintain quality of life. Despite the many attempts to do renal replacement in early part of 20th century, the first successful renal transplant was done in 1954 by Murray among identical twins.

Introduction of calcineurin inhibitor in later part of twentieth century revolutionized the the history of renal transplantion by reducing the short term morbidity and mortality. However the patients receiving calcineurin inhibitor were under the risk of calcineurin inhibitor nephrotoxicity in long run. The chronic nephrotoxic effects of calcineurin inhibitors associated with the renal parenchymal damage plays a major role in the pathogenesis of chronic renal dysfunction. Calcineurin inhibitor toxicity clinically characterized by tremor, hypertension, hypertrichosis and gum hypertrophy, biochemically by raising creatinine (graft dysfunction), hyperglycemia, hyperkalemia and hyperuricemia and histopathologicaly by isometric vacuolization, arterial nodular hyalinosis and striped fibrosis.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INFORMATION SHEET

We are conducting a study on A STUDY ON CLINICAL, BIOCHEMICAL, DRUG TROUGH LEVEL AND HISTOPATHOLOGICAL CORRELATION OF CALCINEURIN INHIBITOR (CNI) TOXICITY IN RENAL ALLOGRAFT RECEPIENT at Department of Nephrology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-600003.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the Participant **Signature of the Investigator**

Institution
Date :

PATIENT CONSENT FORM

Study Details: A STUDY ON CLINICAL, BIOCHEMICAL, DRUG TROUGH LEVEL AND HISTOPATHOLOGICAL CORRELATION OF CALCINEURIN INHIBITOR (CNI) TOXICITY IN RENAL ALLOGRAFT RECEPIENT

Study Centre: Department of Nephrology,
Rajiv Gandhi Government General Hospital, Madras
Medical College, Chennai-600 003.

Patient may check (✓) these boxes

I confirm that I have read and understood the Information Sheet for the above study. I have- had the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

I understand that the Clinical study personnel, the Ethics Committee and the Regulatory Authorities will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

I hereby consent to participate in this study. ☐

Signature of Investigator Thumb Impression of Patient

Patient Name/ Address

Name of the Investigator

Institution

ஆராய்ச்சி தகவல் தாள்

சென்னை அரசு பொது மருத்துவமனை ° À] Ö } µP ©õØÖ AÖ ø Áa] Qa ø Œ öŒ # x öPõ s h @ | õ ¯ õ Î PÒ EmöPõÒÐ ® PõÀ] { ³ › ß CßQ ¤ mhõº © ¸ z x P Î ÚõÀ HØ£ k ® Â ø Í ÄPÒ & J ¨ £õ # Ä.

நீங்கள் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் பங்கேற்பதால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிக்கப்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியின் முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போதோ அல்லது ஆராய்ச்சியின் முடிவின் போதோ தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கோள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

சுய ஒப்புதல் படிவம்

ஆய்வுசெய்யப்படும்தலைப்பு

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ஆராய்ச்சி நிலையம்:]Ö}µP மருத்துவத் துறை,
இராஜீவ் காந்தி அரசு பொது மருத்துவமன
மற்றும் சென்னை மருத்துவக்கல்லூரி, சென்னை – 600 003.

பங்கு பெறுபவரின் பெயர்: **உறவு முறை:**

பங்கு பெறுபவரின் எண்:

பங்கு பெறுபவர் இதனை (√) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களைக் கேட்கவும், அதற்கான தகுந்த விளக்கங்களைப் பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகத்தான் பங்கேற்கிறேன். எந்தக் காரணத்தினாலோ எந்தக் கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்மந்தமாகவும், மேலும் இது சார்ந்தஆய்வு மேற்கொள்ளும்போதும், இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளைப் பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்துகொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும், அதைப் பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்குக் கொடுக்கப்பட்ட அறிவுரைகளின் படி நடந்துகொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறாக நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு மருத்துவப் பரிசோதனை, இரத்தப் பரிசோதனை பரிசோதனை செய்து கொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம் ..... தேதி .....

கட்டைவிரல் ரேகை:

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் .....தேதி .....

ஆய்வாளரின் பெயர் .....

PROFORMA

RECIPIENT			DONOR			
			DECEASED	LIVE RELATED		
NAME	AGE/SEX	D O TX	AGE/SEX	AGE/SEX	RELATION	DISCHARGE CREATININE

0-3, 3-6, 6-9 , MORE THAN 9 MONTHS

TRANSPLANT AGE (IN MONTHS)	
CNI	
DOSE	
TROUGH LEVEL	
ELEVATED/NORMAL	
CLINICAL	TREMOR
	PARESTHESIA
	HYPERTRICHOSIS
	GUM HYPERTROPHY
	HYPERTENSION
BIOCHEMICAL	CREATININE
	SODIUM
	POTTASIUM
	CHOLESTEROL
	NODAT
	ISOMETRIC VACUOLIZATION
	MEDULLARY HYALINISIS
	GLOMERULOSCLEROSIS
	MES.MAT. EXPANSION
	TMA
	CNI TOXICITY

	RECEIPIENT						DONOR														CLINICAL FEATURE						INVESTIGATION							BIO		
							DD		LR																											
Sl.No.	name	age	sex	nkd	D OF TX	PERIOD	AGE	SEX	RELATION	AGE	SEX	DD/LD	INDUCTION	DIS CR	TX AGE(M)	CNI	DOSE	TROUGH	TOXIC LEVEL	ACTION	TREMOR	P aesthes	hypertric	htn	gum		CR 3		SADIUM	POT	CHOLEST	NODAT	ISO	ME HY	INT FIB
1	P	26	M	IGA CGN	6/18/2012	18			FATHER	51	M	LD	N	0.8	3	CSA	250	295	YES	250>225	Y	N	N	N	N	YES	0.8	N	134	3.7	156	N	N	N	N
2	K	22	M	HORSE SHOE	6/19/2012	18			mother	45	F	LD	N	2.1	1	CSA	225	215	NO		N	N	N	N	N	NO	1.1	N	142	4.2	156	N	N	N	N
3	L	42	M	CGN	6/21/2012	18			SPOUSE	41	F	LD	N	1.7	1	TAC	5	6	NO	5>4.5	Y	N	N	Y	N	YES	1.8	N	138	3.8	145	N	N	N	N
4	R	47	M	DKD	6/22/2012	18	25	M				DD	N	1	1	TAC	6	4.1	NO		N	N	N	N	N	NO	1.1	N	130	4.2	206	N	N	N	N
5	C	47	M	CGN	6/26/2012	18			SPOUSE	36	F	LD	N	0.9	1	TAC	5	5.8	NO		N	N	N	N	N	NO	1	N	135	4.2	156	N	N	N	N
6	R	27	M	CGN HCV	7/7/2012	17	25	M				DD	N	1.3	1	CSA	250	260	YES	250>225	N	N	N	N	N	NO	1.5	Y	140	4.4	165	N	N	N	N
7	M	44	M	CGN	7/9/2012	17			WIFE	39	F	LD	N	1	1	TAC	6	5.5	NO	6>5	N	N	N	Y	N	YES	1.7	Y	142	4.6	167	N	N	N	N
8	M	40	M	CGN	7/10/2012	17			MOTHER	56	F	LD	N	1.2	3	CSA	250	220	YES		N	N	N	N	N	NO	1.1	N	136	3.9	210	N	N	N	N
11	M	32	M	NK	7/16/2012	17	14	M				DD	N	1.4	2	TAC	7	8.6	YES	7>6	Y	N	N	Y	N	YES	1.4	N	145	4.5	180	N	N	N	N
12	M	45	M	CGN	7/17/2012	17			WIFE	35	F	LD	Y	1.2	1	TAC	6	28	YES	4>3>1.5	N	Y	N	Y	N	YES	1.4	Y	138	4.2	185	Y	N	N	N
13	B	22	F	NK	7/19/2012	17			mother	45		LD	N	1	1	CSA	275	234	NO	275>250	Y	N	N	Y	N	YES	1.4	Y	140	4.2	160	N	N	N	N
14	S	46	M	NK	7/28/2012	17	42	M				DD	Y	2	1	TAC	5	14.7	YES	5>4	N	N	N	Y	N	YES	2.9	Y	135	4.5	145	N	Y	Y	N
15	M	17	M	CGN	8/14/2012	16			MOTHER	36	F	LD	N	1	1	CSA	225	215	NO		N	N	N	N	N	NO	1.1	N	142	4.2	156	N	N	N	N
17	M	43	M	CGN	8/23/2012	16			SISTER	50	F	LD	N	1.2	1	CSA	275	245	NO		N	N	N	N	N	NO	1	N	132	3.7	186	N	N	N	N
18	D	26	M	CGN	8/28/2012	16			FATHER	55	M	LD	N	1.3	2	CSA	375	240	YES	375>350	y	N	N	N	N	YES	1.3	N	136	4.6	196	N	N	N	N
19	S	22	M	CGNANCA NEG	8/31/2012	16			MOTHER	45	F	LD	N	1.2	1	CSA	300	204	NO		N	N	N	N	N	NO	0.6	N	145	4.1	158	N	N	N	N
20	R	35	M	CGN	9/11/2012	15			SPOUSE	33	F	LD	Y	1.2	1	TAC	6	5.5	NO	6>5	N	N	N	Y	N	YES	1.7	Y	142	4.6	167	N	N	N	N
21	E	28	M	NK	9/20/2012	15			MOTHER	55	F	LD	N	2.1	1	CSA	275	197	NO	275>250	Y	N	N	Y	N	YES	2.8	Y	140	3.9	168	N	N	N	N
22	K	49	F	NK	9/21/2012	15	28	M				DD	Y	1.2	1	TAC	5	6	NO		N	N	N	N	N	NO	1.1	N	136	3.8	156	N	N	N	N
23	S	17	M	CGN	9/24/2012	15			FATHER	55	M	LD	N	0.8	3	CSA	225	236	YES	225>200	Y	N	N	N	N	YES	1.8	Y	140	3.9	168	N	N	N	N
24	V	34	M	CIN	9/25/2012	15			SPOUSE	28	F	LD	Y	1.3	3	TAC	6	8.6	YES	6>5	Y	N	N	N	N	YES	1.4	N	138	3.8	170	N	N	N	N
25	S	40	M	NK	9/30/2012	15	40	M				DD	N	0.9	1	TAC	3.5	4.7	NO		N	N	N	N	N	NO	0.9	N	145	3.7	189	N	N	N	N
27	N	20	F	CGN	10/9/2012	14			mother	50	F	LD	N	1	1	CSA	275	234	NO	275>250	Y	N	N	Y	N	YES	1.4	Y	140	4.2	160	N	N	N	N
28	D	56	M	NK	10/12/2012	14	35	M				DD	Y	1.2	2	TAC	5	4.5	NO		N	N	N	N	N	NO	1	N	142	3.8	187	N	N	N	N
29	S	22	M	IGA CGN	10/16/2012	14	20	M				DD	Y	1.4	3	TAC	6	23.3	YES	4	Y	N	N	N	N	YES	0.8	N	140	3.7	168	N	N	N	N
30	V	27	M	CGN	10/18/2012	14			MOTHER	55	F	LD	N	1.9	1	CSA	300	235	NO	300>275	Y	N	N	Y	N	YES	2.2	Y	140	3.5	145	N	N	N	N
32	S	40	M	CGN	10/30/2012	14			mother	55	F	LD	N	1	3	CSA	275	196	NO		Y	N	N	N	N	YES	1.4	Y	146	3.8	138	N	N	N	N
33	J	21	F	CGN	11/9/2012	13			MOTHER	40	F	LD	N	1.7	1	CSA	225	215	NO		N	N	N	N	N	NO	1.1	N	142	4.2	156	N	N	N	N
34	E	27	M	MN CGN	11/15/2012	13			SISTER	45	F	LD	N	0.9	1	CSA	275	234	NO	275>250	Y	N	N	Y	N	YES	1.4	Y	140	4.2	160	N	N	N	N
35	M	50	M	CGN	11/20/2012	13			SISTER	55	F	LD	N	1.2	1	CSA	250	240	NO		N	N	N	N	N	NO	1	N	145	3.9	190	N	N	N	N
37	M	43	M	CGN	11/27/2012	13	43	M				DD	Y	1	1	TAC	6	5.5	NO	6>5	N	N	N	Y	N	YES	1.7	Y	142	4.6	167	N	N	N	N
38	M	36	M	NK	11/27/2012	13			MOTHER	55	F	LD	N	1.3	1	CSA	350	143	NO	350>325	Y	N	N	Y	N	YES	1.7	Y	138	3.8	160	N	Y	N	N
40	R	30	M	NK	12/11/2012	12			MOTHER	55	F	LD	N	1.2	1	CSA	225	240	NO		N	N	N	N	N	NO	1	N	138	3.8	190	N	N	N	N
41	K	34	F	CGN	12/18/2012	12			mother	54	F	LD	N	1.1	1	CSA	300	281	YES	300>275	Y	N	N	N	N	YES	1	N	136	4.2	210	N	N	N	N
42	K	45	F	NK	12/20/2012	12	50	M				DD	Y	1.5	1	TAC	6	5.5	NO	6>5	N	N	N	Y	N	YES	1.7	Y	142	4.6	167	N	N	N	N
44	P	18	M	NK	12/24/2012	12			FATHER	54	M	LD	N	1	2	CSA	275	330	YES	275>225	N	N	N	N	N	NO	2.4	Y	145	4.5	167	N	N	N	N

45	E	29	M	NK	1/22/2013	11			SPOUSE	26	F	LD	Y	1.1	1	TAC	7	5.6	NO		N	N	N	N	N	NO	1.2	N	138	3.8	167	N	N	N	N
46	P	25	F	CGN	1/27/2013	11	14	M				DD	Y	1	1	TAC	6	5.5	NO	6>5	N	N	N	Y	N	YES	1.7	Y	142	4.6	167	N	N	N	N
47	M	24	M	CGN	1/28/2013	11			MOTHER	46	F	LD	N	1.2	3	CSA	350	202	YES	350>250	Y	N	N	N	N	YES	1.4	Y	145	3.9	156	N	N	N	N
48	M	20	F	CGN	1/31/2013	11			FATHER	55	M	LD	N	1.1	2	CSA	225	242	YES		N	N	N	N	N	NO	1	N	138	3.6	178	N	N	N	N
49	S	33	M	NK	2/7/2013	10			mother	52	F	LD	N	1.8	1	CSA	350	278	YES	350>300	Y	N	N	Y	N	YES	2.3	Y	143	3.2	216	N	N	N	N
50	V	26	M	NK	2/18/2013	10			MOTHER	40	F	LD	N	1.6	1	CSA	325	91	NO	325>300	Y	N	N	Y	N	YES	1.7	N	138	3,8	196	N	Y	Y	N
51	P	36	M	CGN	2/28/2013	10			MOTHER	50	F	LD	N	1	1	CSA	300	178	NO	300>275	Y	N	N	Y	N	YES	1.2	N	143	3.7	210	N	Y	N	N
52	B	31	M	HBV CGN	3/12/2013	9			SPOUSE	25	F	LD	Y	1	2	TAC	5	3.4	NO	5>4.5	Y	N	N	Y	N	YES	1.1	N	142	4.6	189	N	N	N	N
53	S	31	M	NK	3/17/2013	9	45	M				DD	Y	1.6	1	TAC	6	5.5	NO	6>5	N	N	N	Y	N	YES	1.7	N	142	4.6	167	N	N	N	N
54	E	42	M	NK	3/17/2013	9	42	M				DD	Y	1.9	1	TAC	5	6	NO		N	N	N	N	N	NO	1.1	N	136	3.8	156	N	N	N	N
55	R	32	M	NK	3/20/2013	9	30	M				DD	Y	0.9	1	TAC	3.5	4.7	NO		N	N	N	N	N	NO	0.9	N	145	3.7	189	N	N	N	N
56	J	28	M	CGN	3/25/2013	9			MOTHER	55	F	LD	N	1.6	1	CSA	350	290	YES	350>325	N	N	N	Y	N	YES	1.6	N	130	3.8	187	N	N	N	N
57	E	36	M	CIN	3/26/2013	9			SISTER	42	F	LD	N	1	3	CSA	300	137	NO	300>250	Y	N	N	N	N	YES	1.5	Y	138	3.9	196	N	N	N	N
58	M	22	M	CGN	3/28/2013	9			FATHER	50	M	LD	N	1.8	1	CSA	350	209	NO	350>300	N	N	N	N	N	NO	2.2	Y	143	3.6	210	N	Y	N	N
59	A	24	M	HBV CGN	4/2/2013	8	53	M				DD	Y	1	3	TAC	4	2	NO		N	N	N	N	N	NO	1.2	N	140	3.9	156	N	N	N	N
60	M	34	M	CGN	4/4/2013	8			SPOUSE	24	F	LD	N	1	1	TAC	6	2	NO	6>5>4>3	Y	N	N	N	N	YES	1.4	Y	130	3.8	187	N	Y	N	N
61	H	24	F	NK	4/9/2013	8	24	F				DD	Y	1.3	1	TAC	6	5.5	NO	6>5	N	N	N	Y	N	YES	1.7	Y	142	4.6	167	N	N	N	N
62	A	50	M	CIN	4/16/2013	8			SPOUSE	40	F	LD	Y	1	3	TAC	4	5.8	NO		N	N	N	N	N	NO	1	N	147	4.7	190	N	N	N	N
63	N	35	F	NK	4/25/2013	8	38	M				DD	Y	3.2	1	TAC	6	5.5	NO	6>5	N	N	N	Y	N	YES	1.7	N	142	4.6	167	N	N	N	N
64	P	55	M	CIN	4/26/2013	8			SPOUSE	50	F	LD	Y	1	3	TAC	7	7.5	YES	7>6.5	Y	N	N	N	N	YES	1.2	N	142	4.2	187	Y	N	N	N
65	P	28	M	CGN	4/30/2013	8			FATHER	52	M	LD	N	1.2	2	CSA	225	210	YES	225>175	Y	N	N	Y	N	YES	1.4	N	146	3.5	167	N	N	N	N
67	S	30	M	NK	5/14/2013	7			SPOUSE	23	F	LD	Y	1	3	TAC	4	4	NO		N	N	N	N	N	NO	1.1	N	137	3.7	180	Y	N	N	N
70	R	28	M	NK	5/28/2013	7			SPOUSE	25	F	LD	Y	1.1	3	TAC	4	5.2	NO	4>3	Y	N	N	N	N	YES	1.2	N	140	4.1	196	N	N	N	N
71	E	43	M	NK	6/5/2013	6	23	M				DD	Y	0.9	2	TAC	4	4.5	NO		N	N	N	N	N	NO	1	N	135	3.2	187	N	N	N	N
74	S	27	M	CGN	6/18/2013	6			MOTHER	51	F	LD	N	1.4	1	CSA	250	155	NO		N	Y	N	N	N	YES	1.5	N	146	3.9	167	N	N	N	N